MEDICINAL USES OF PLANTS; PROTECTION FOR PLANTS UNDER THE ENDANGERED SPECIES ACT

RING

RE THE

SUBCOMMITTEE ON ENVIRONMENT
AND NATURAL RESOURCES

OF THE

COMMITTEE ON
MERCHANT MARINE AND FISHERIES
HOUSE OF REPRESENTATIVES

ONE HUNDRED THIRD CONGRESS

FIRST SESSION

ON

MEDICINAL USES OF PLANTS; CURES MADE POSSIBLE BY CERTAIN PLANTS AND DISCUSSION OF WHETHER THE ENDANGERED SPECIES ACT ADEQUATELY PROTECTS PLANTS

NOVEMBER 9, 1993

Serial No. 103-74

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MEDICINAL USES OF PLANTS; PROTECTION FOR PLANTS UNDER THE ENDANGERED SPECIES ACT

TUESDAY, NOVEMBER 9, 1993

HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON ENVIRONMENT AND NATURAL RESOURCES,
COMMITTEE ON MERCHANT MARINE AND FISHERIES,
Washington, DC.

The Subcommittee met, pursuant to call, at 10:06 a.m., in room 1334, Longworth House Office Building, Hon. Gerry E. Studds [chairman of the Subcommittee] presiding.

Present: Representatives Studds, Hochbrueckner, Pallone, Furse, and Taylor.

Staff Present: Gina DeFerrari and Lesli Gray, Professional Staff; Marvadell Zeeb, Clerk; Laurel Bryant, Minority Professional Staff; Harry Burroughs, Minority Staff Director; and Cynthia Wilkinson, Minority Chief Counsel.

Mr. STUDDS. The Subcommittee will come to order. Let me observe at the outset that the photographs on the wall here, newly arrived, are from an exhibit by Mary L. Levine called Rare Beauty, America's Endangered Plants. This exhibit is sponsored by the National Fish and Wildlife Foundation. These photographs are on loan to the Committee through the end of the year.

I guess it is the way to reach even the most hardhearted of our brethren when it comes to endangered flora, not that we have any of those.

STATEMENT OF HON. GERRY E. STUDDS, A U.S. REPRESENTATIVE FROM MASSACHUSETTS, AND CHAIRMAN, SUBCOMMITTEE ON ENVIRONMENT AND NATURAL RESOURCES

This morning, the Subcommittee meets to examine the medicinal value of plants and the array of cures they may hold for all the things that ail us. We will also discuss the extent to which endangered plants are protected under the Endangered Species Act (ESA).

Plants have been used for medicinal purposes for a millennium. Today, one need only look as far as his or her own medicine cabinet to locate a product derived from plants—aspirin. And there are many other examples.

Anyone who has felt the immediate relief of the aloe vera plant on a blistering sunburn can certainly appreciate its healing quali-

ties. Thanks to the rosy periwinkle, childhood leukemia and Hodgkin's disease are largely curable.

Taxol, a medicinal product derived from the Pacific yew tree, has offered hope to thousands of women suffering from ovarian cancer. And kudzu, a notorious exotic species in this country, which made an appearance in our hearing room a few weeks ago, is used by the Chinese to treat alcoholism. Our own scientists are now exploring its potential with positive results.

Perhaps most encouraging is that developments such as these represent only a tiny fraction of the answers that may yet be found in the still largely unexplored plant kingdom.

Sadly, however, the untapped potential of many plants to provide cures for diseases such as AIDS, cancer, and Alzheimer's may be lost as plant species go the way of the dodo bird and the passenger pigeon. As these species disappear, we lose forever the opportunity to explore their medicinal values.

Currently, the Endangered Species Act provides far fewer protections for plants than for animals. As we proceed with the reauthorization of the Act, we must determine whether adequate protection is being provided to our native flora. The consideration that we give these species today may very well hold the key to our survival tomorrow.

Mr. STUDDS. We will begin our panel of witnesses with Dr. Tom Eisner from Cornell University, renowned for his work with natural chemicals and their medicinal applications.

Are there additional opening statements?

The gentlewoman from Oregon.

STATEMENT OF HON. ELIZABETH FURSE, A U.S. REPRESENTATIVE FROM OREGON

Ms. FURSE. Mr. Chairman, I am very pleased to be here this morning to hear the testimony on this very important topic. As the saying goes, the first rule of tinkering is not to throw away any of the parts. How are we to know which of the parts are critical to make the whole system work?

Such wisdom applies to the protection of species. We don't know enough about our natural systems to understand the potentially dire consequences of diminishing our biodiversity. For that reason, we should certainly save all of the parts.

The subject of this hearing, the medicinal potential of plants, is another persuasive reason not to throw away any of the parts. The Pacific yew tree which you referred to, Mr. Chairman, comes from my region of Oregon. We do know that there is direct potential for ovarian cancer treatment through that tree. Yet that tree was threatened with clear-cutting and there was a potential for losing the Pacific yew.

I look forward to the testimony of these experts regarding the measures they feel are necessary to ensure that we more fully preserve and explore our opportunity to seek and discover new medicines in plants.

Thank you.

Mr. STUDDS. I thank the gentlewoman.

Mr. STUDDS. Let me say to our witnesses that, as always, we are under a regrettable press for time here. We have asked each of you to confine your oral testimony to no more than five minutes. Your written testimony will appear in its entirety in the record.

Mr. STUDDS. As usual, we apologize in advance for the barbarity of the light system you see in front of you. When the yellow lights goes on, that is your one-minute warning, and when the red light goes on, you are done. We apologize for the brutality of that.

We will hear from all six of you before we go to questions. Our first witness, Dr. Thomas Eisner of Cornell, I am told is one of the best leading arguments against our five-minute rule. I profusely apologize. I understand I will regret having announced the rule in the first place. Dr. Eisner, Director of the Cornell Institute for Research and Chemical Ecology, welcome.

STATEMENT OF DR. THOMAS EISNER, DIRECTOR, CORNELL INSTITUTE FOR RESEARCH AND CHEMICAL ECOLOGY, CORNELL UNIVERSITY, ITHACA, NEW YORK

Mr. EISNER. Thank you sir. My name is Thomas Eisner. I am Professor of Biology at Cornell University and Director of Cornell's Institute for Research in Chemical Ecology. I am a member of the National Academy of Sciences, former President of the American Society of Naturalists, and former Chairman of the Section of Biology of the American Association for the Advancement of Science, the largest scientific organization in the United States.

I am a chemical ecologist. I work on the chemicals of nature. I try to isolate new substances from organisms and attempt to determine how these substances function and how they might be put to applied use.

Humans have benefited from natural substances since time immemorial. Nature has provided us with spices and perfumes, glues and solvents, countless agrochemicals such as fungicides, pesticides, and insect repellents—and, most importantly, it has given us medicinals. Fully one-third of medical prescriptions given out annually in the United States are based on substances derived from nature or synthesized in imitation of natural substances. "Miracle drugs" continue to be discovered to this very day. Examples of recent additions to our medical arsenal include: Vincristine and vinblastine, anticancer agents from a periwinkle plant; avermectins, worm-killers from molds; and cyclosporin and FK 506, immunosuppressants used in organ transplants, also from molds.

As a chemical ecologist, I have come to realize that the vast majority of natural chemicals remains to be discovered. Of the 30 million species estimated to inhabit our planet, most have yet to be described, let alone studied chemically. Only about 5 percent of species have been formally named; the fraction that has been studied chemically is orders of magnitude smaller.

I am also aware that species are disappearing faster than we are able to examine them chemically. The chemical treasury of nature is literally disappearing before we have had a chance to assess it. I find that reality disconcerting. We cannot afford, in years ahead, to be deprived of the inventions of nature. Chemicals such as ivermectin and FK 506 could not have been designed by human ingenui-

ty—this is important to realize. Both compounds were totally unforeseen in chemical structure and therapeutic action. What nature holds in store will take centuries to discover. Preserve it now, and we will continue uncovering the likes of FK 506 and ivermectin. Allow it to vanish, and we will forever be impoverished.

To the extent that the Endangered Species Act provides a means for monitoring the decline of biodiversity in the United States and a mechanism for saving important habitats where species are threatened, the Act fulfills a vital function. In my judgment, its reauthorization should be a matter of the highest national priority.

The current hearings, I understand, are intended to focus on plants, and specifically on the medicinal value of plants. I would therefore like to deal briefly with several questions that are often raised in connection with the Endangered Species Act, questions that are particularly relevant to plants, and need to be addressed in chemical terms.

Why, for instance, should more than one population of a plant be saved? The answer is that, at different portions of their range, organisms tend to differ genetically, and consequently, chemically. Compounds produced by a plant in New England may be absent from its relatives in Georgia. Preserving more than one population of a species is prudent to maximize the chance of discovering new chemicals.

Why, one is also asked, should a species be preserved in the wild? Could it not be maintained in an artificial setting? Species in unnatural settings may not produce all the chemicals they synthesize in the wild. Plants, in particular, may produce specific compounds only when induced to do so by certain environmental factors, such as infection, parasites, or grazers. Compounds that they produce when thus challenged are often the very ones likely to prove useful to humans. There is, therefore, no appropriate alternative to preserving species in the wild.

Does a plant lose its value once it has been examined chemically? Does it matter if it then becomes extinct? Our chemical knowledge of organisms is never exhaustive. Any species contains hundreds of compounds of potential interest. In our chemical searches today we find only what current technology enables us to detect and what our state of knowledge tells us to seek. Even species that are well known chemically are bound to contain unknown substances discoverable only by future techniques. Species, in nature, do not become chemically obsolete.

Species will need to be preserved also for their intrinsic genetic worth. Genes, nowadays, can be envisioned as transferable items. It is becoming increasingly possible to transmit biological capabilities from one organism to another by transference of genes. Genes which in one species, say a plant, encode for production of a hard-to-synthesize medicinal, could some day be transferred to a readily cultured microbe, which would then become the vehicle for industrial production of the compound. If for no other reason than to keep such genetic options open, species need to be preserved. Biotechnology is only now coming of age. We are only beginning to appreciate its long-range promise.

My final point concerns some remarkable recent scientific findings which suggest that gene flux, the transference of genes from

species to species, such as we had thought to be possible only at the hands of the biotechnologist, occurs also as a matter of course in nature. Evidence has been uncovered that such "horizontal gene transfer" can occur between microorganisms, from microorganism to plant, from virus to insect, and even perhaps from insect to insect by way of a third species. This work is only now unfolding but appears to be of the utmost importance.

Genes are traditionally envisioned to flow strictly from parents to offspring and to provide the basis of heredity. That they should also at times flow between unrelated organisms revolutionizes our view of nature and of how we picture evolution unfolding over time. It tells us, basically, that there is much more to nature's genetic ingenuity than we had imagined, and therefore much more to be learned from nature, and to be reaped from the biotic world, over the long term. It tells us further that if we are to derive these benefits, we will need to preserve species as parts of functional ecosystems and not as museum pieces.

The Endangered Species Act is the most comprehensive and powerful piece of environmental legislation yet enacted by the United States. Although it falls short in that it does not provide the tools to prevent endangerment, it is of unquestionable merit. Its reauthorization is essential.

Thank you.

Mr. STUDDS. Thank you, sir.

I don't know what kind of serendipity it is, but the lights promptly broke upon your being introduced. You should have taken advantage of the awesome power that you have.

Until such time as they may be corrected, I will take it upon myself and if necessary do my own imitation of a light.

Thank you.

Next, Dr. Grever of the National Cancer Institute.

STATEMENT OF DR. MICHAEL GREVER, ASSOCIATE DIRECTOR, DEVELOPMENTAL THERAPEUTICS PROGRAM, THE NATIONAL CANCER INSTITUTE, BETHESDA, MARYLAND

Dr. GREVER. Good morning Mr. Chairman and Members of the Committee. I am Dr. Michael Grever, Associate Director for the Developmental Therapeutics Program of the National Cancer Institute's Division of Cancer Treatment, at the National Institutes of Health.

With me today are Dr. Gordon Cragg, Chief of DTP's Natural Products Branch, and Dr. Francesca Grifo, a Program Manager in the International Studies Branch of the Fogarty International Center.

Thank you for the opportunity to appear before you today to discuss the NCI's efforts to locate and develop medicinal compounds from plants to combat cancer and HIV infection and its sequelae.

NCI is exploring and supporting a broad spectrum of ways to combat these two diseases, from prevention and diagnosis through treatment and rehabilitation and psychosocial care of patients.

Drug development from natural products is just one avenue of emphasis; but until we can completely prevent cancer or HIV infection from occurring, it is an extremely important part of our

effort to develop and design more effective and less toxic treatments for these fatal illnesses.

The NCI has played a crucial role in cancer drug discovery and development since 1955. Following the recognition of AIDS as a lethal disease, the NCI's infrastructure for drug discovery and development were enlisted in 1987 to assist in the important task of identifying promising new therapeutic products for this disease.

The long history of screening for anti-cancer "lead" agents served as a model to develop a similar tool to identify lead chemical structures of potential benefit for patients with AIDS.

The NCI's laboratory-based efforts to develop newer approaches to drug treatment have been responsible for producing many of the currently available therapeutic products, e.g., AZT, ddI, and ddC. Additional agents are currently under development with a major objective being the expeditious preclinical evaluation to provide safe and effective novel therapeutic products.

Natural products play an essential role in both traditional and modern medicine. While plants and microbial sources have formed the basis for discovering many lead chemicals with therapeutic use, marine organisms and many untapped microbes and plants remain as potential sources of true chemical diversity.

Many of the recent natural product discoveries were derived from plants: taxol, camptothecin, and homoharringtonine have had utility in the treatment of patients with cancer. Likewise, additional promising plant products have been identified as potentially useful for the treatment of AIDS, including michellamine, calanolide, costatolide, and conocurvone.

Since 1986, there has been a renewed commitment to pursue the search for active chemical leads within nature. Certainly, the diversity and complexity of chemical structures within nature outstrip the efficiency and imagination of even our most talented chemists.

We rely on nature to provide the lead chemical structures which can be subsequently optimized by natural product and medicinal chemists. The NCI has taken extensive, bold measures to collect diverse samples of natural products from the forests, microbial sources, and the sea.

Our collectors are highly qualified scientists committed to conservation and preservation of biodiversity. Candidate drug discoveries have already resulted in concrete efforts to preserve natural habitats.

The NCI has taken the initiative to develop mechanisms to protect the rights of developing countries that have opened their borders to this critically important mission. We have obtained endorsement from our scientific board of advisors to use the material collected from Asia, Central and South America, and Africa to search for potentially effective agents for the treatment of cancer, AIDS, and, importantly, those diseases of importance to the host countries.

The NCI collaborated with the Agency for International Development, the National Science Foundation, and the Fogarty International Center at NIH to sponsor a workshop on preservation of biodiversity.

Issues of critical importance ranging from protection of the intellectual property rights of the supplying country to the responsible methods used to scale up procurement of crude material from the environment were addressed.

The efforts of the NIH, the Agency for International Development, the National Science Foundation, and the International Fogarty Center to protect the interests of developing nations have been internationally recognized, and complemented by collaborative research projects.

The NCI has dedicated intramural scientists who are working to characterize the chemical entities responsible for the desired biological effect in the drug screens, i.e., anti-tumor or anti-HIV activities.

I must emphasize, however, that evidence of such anti-tumor or anti-HIV activity in a test tube does not guarantee that a specific agent will become a viable drug candidate. Extensive work is needed to bridge the gap between the initial observation of interesting *in vitro* activity to the point of clinical delivery.

Resources are needed for initial collection of raw material, recollection of promising lead material, processing and chemical isolation of purified chemical agents, formulation for clinical delivery, and preclinical pharmacologic and toxicological evaluation prior to human administration.

We understand that a sense of urgency must be conveyed to those entrusted with these tasks, and also emphasize that concern relating to safety must be paramount in preparing agents for eventual human administration.

It is a sense of urgency that prompted the NCI to share its Natural Product Repository with extramural, academic and pharmaceutical investigators working to identify promising new agents for these fatal diseases.

This effort will potentially reduce the uncoordinated collection projects within areas already carefully evaluated by NCI collector scientists.

In addition, we have strongly supported the National Cooperative Drug Discovery Group Program to enhance the likelihood of successful drug discovery. Based on this model, which finances combined efforts to coordinate academic, pharmaceutical or industrial, and governmental resources, the NIH has worked with other Federal agencies to encourage a program for international drug discovery groups searching for therapeutic advances in these fatal diseases.

The unique circumstances surrounding the production of a given natural product with the environment demonstrates the absolute necessity for preservation and conservation of biodiversity. We firmly believe that nature's rich treasure chest of unique chemical compounds must be preserved for the ultimate benefit of mankind.

We appreciate the opportunity to answer any questions.

Mr. STUDDS. This is an exercise in humility for us. We are in awe of people who know things. Thank you.

[The statement of Dr. Grever can be found at the end of the hearing.]

Mr. STUDDS. Next, Mrs. Elaine B. Forman from Potomac, Maryland, who is a cancer patient with experience in the subject matter of this hearing.

STATEMENT OF ELAINE B. FORMAN, CANCER PATIENT TREATED WITH TAXOL, POTOMAC, MARYLAND

Ms. FORMAN. When you look at me, I think you see a healthy woman and for now I do feel well. But if it were not for the National Institutes of Health taxol program I would probably not be alive today. I am a cancer survivor, in remission for a little more than a year now.

In May of 1991, after four months of what I view as the most horrible tests known to man, all of which turned out negative, only after surgery, I was diagnosed with ovarian cancer. The surgeon told my children I had six months to live.

I was treated with the traditional chemotherapy, cisplatin and cytoxin. The treatment was difficult and about two-thirds through, it was evident that I was not responding. What supposedly was the best treatment available to ovarian cancer patients just had not worked for me.

I would like to tell you something about myself before cancer.

I call myself a geriatric jock. I was involved more than casually in athletics, not just since the health craze but what seems like forever. I am happy to say that after treatment and as soon as my blood levels returned to normal I went back to my daily exercise routine. In December, it will be a year.

As for nutrition, it had always been one of my greatest concerns. I know about fibers, vegetables and fruits. I have run a vegetarian household since 1977. When I would go out with friends, they would jokingly say, "We have to behave ourselves now that we are with Lainie." I don't smoke and I have an occasional glass of wine with dinner.

I get annual physicals. My doctor knows me very well; he delivered my children. I have been "in perfect health". There is longevity on both sides of my family. My 86-year-old mother moved to this area a year ago and is independent and well. My father died at 89. Moreover, there is no history of cancer in my family.

I consider myself a contented person. I did have a tragedy six years ago. My husband died. It was not easy for the family after that, but my children completed their education. I stayed in our home and was able to continue with my business. I am fortunate to have many friends and have remained active and busy during all my treatments.

I would say I was a low-risk person.

But October of 1992, having failed to respond to chemotherapy, and feeling really sick, I knew I was in a bad place. Other drug treatments were suggested, but I knew I had the best there was, and that these would be ineffective.

I heard about taxol. I had even tried to get in a program for first-line treatment, but I didn't fit the protocol. It was not until I really needed taxol that I realized how difficult it was to get. Fortunately, taxol is now available for ovarian cancer treatment for all women.

My son came home to be my caretaker and investigated every taxol program in the area. He became very informed. I used every contact I had. After one denial and attempts to enter other programs, I finally did get into the NIH taxol program. It was the best thing that ever happened to me.

I cannot rave enough about NIH. Even though it was the most difficult and scary time of my life, my experience at NIH was wonderful. I love everyone. I felt good about being a so-called guinea pig.

I am not saying that it was easy. I discovered that fighting cancer is a full-time job, but it was possible to handle the treatment and still have an OK life-style, especially as a patient at NIH, with all the caring personnel and extensive support.

I have been lucky so far but I have met a lot of women in the program that may not have had such a healthy time as I have had, and most of them feel the same way as I do. Fortunate for every day. When people tell me that I am remarkable, I always say, "I know a lot of remarkable people."

Since remission, I have gone back to my normal life. I serve on the District of Columbia board of Share Our Strengths, Taste of the Nation. I am currently teaching cooking to a group of WIC mothers, emphasizing nutrition, economy, and how to vary the use of WIC commodities. This, too, is an SOS program, Operation Frontline.

I chair the World Hunger Committee of the International Association of Culinary Professionals Foundation, and in April I was awarded their Humanitarian Award for contributing to the Organization's understanding of world hunger.

I also at this time sit on the board of Nurture, the Center to Prevent Child Malnutrition, and have been appointed to the board of World Food Day.

Not only am I a living person, continuing to make a contribution, but also a mother, a daughter, a head of a household—all as a cancer survivor.

About a year ago I was on a TV show, How'd They Do That?, a story on how taxol was discovered. The director of the show noticed that I live in the woods, as she said, "a tree house," that I had natural wooden floors and natural wooden furniture. She looked around and said, "It is obvious that you love trees. Trees seem to have played an important part in your life."

I cherish the environment and have played my part in protecting it. We can't even kill household pests. My husband liked to tell the story that it was fine to conserve water, but I had so many bricks in the toilets that they did not flush.

Today, I feel very well. I am cautiously optimistic and very aware of the long-term effect of taxol on my cancer, but I am still very happy. There is always hope of a new discovery, a new treatment.

When I was treated with chemotherapy, I used happy experiences in my life as imagery to get me through the not-so-happy times. Ski runs were a favorite trick, and I'd asked my son, Kenan, "Do you think I will ever ski again?" He would answer somberly, "I don't know."

Well, I did get to ski this past March. As he and I were going up a lift on a beautiful, bright sunny day, high in the Rockies, he turned to me and said, "It was all worth this one run."

Thank you.

Mr. STUDDS. Thank you very much. I like your approach to life so much I may consult with you later about NAFTA. I really appreciate your testimony.

Mr. STUDDS. Next is Mr. Steve Brewer of the Monsanto Company.

STATEMENT OF DR. STEVE BREWER, MANAGER, BIOPRODUCTS CHEMISTRY, MONSANTO COMPANY-SEARLE, ST. LOUIS, MISSOURI

Mr. BREWER. Thank you for inviting me to testify before this Committee. My name is Steve Brewer, manager of Bioproducts Chemistry at Monsanto. Monsanto is a worldwide development and manufacturing company of high-value agricultural and chemical products, pharmaceuticals and food ingredients (NutraSweet), with 1992 sales of $7.8 billion. Over the past four years Monsanto has collaborated with the Missouri Botanical Gardens to obtain approximately 10,000 plant samples from the United States and Puerto Rico, which are used in our screening program.

In the document I submitted—I think mine was one of the more extensive ones—you will find a very detailed rationale for why we decided to actually carry out this program. I took a different cut than some of the other people by asking, "Where did the 20 best-selling drugs in the U.S.A. come from and what was the role of natural products in their discovery?" (These drug sales were worth $8 billion in 1988).

[Answer]: All owe much of their origins to natural products research. It is a very convincing story and there is no doubt in our minds that natural products are important and worth investing in. The plants themselves seem to have played a role in the discovery of seven out of twenty of the best-selling drugs in the U.S.; the rest came from microbes and animal tissue. Even snake venom has played its role!

The next is the concept of random screening; where you take a collection of natural products or even synthetic chemicals and you screen for activity. When I looked for the importance of that in the top-20 drugs discovery, it was apparent that maybe 50 percent of them had emerged from this approach of random screening. Other approaches, such as rational chemical synthesis, were important for a quarter of them, and chance observation (an absolutely essential method whereby we make discoveries), were the major ways in which we found the 20 drugs. In Monsanto's plant screening program what happens is that the botanists from the Botanical Gardens have gone to various areas of the United States; they have collected plants. They are returned to us. We grind these plants up and extract them for small molecules which we then screen for pharmaceutical activities using various enzymes and receptors as targets. The rationale is that if you can inhibit their activity, then it should lead to a useful drug.

It is a very, very long haul up to manufacturing and selling a drug. Many chemicals won't make it. They estimate out of the 10,000 active chemicals, you might get five new drugs. So it is a very expensive and very time-consuming effort to actually identify a new potential medicine.

I thought you might also be interested to know that these plants have also been screened for agrochemical uses, and also for the gene screen, where we are attempting to find genes that might be incorporated into plants to increase their resistance to infections. This is a very powerful technique which modern biotechnology is giving us. We are using these programs also for agrochemical discovery.

What do we have so far? Four years into a screening project is still a long way from the 10 to 15 years it will take us to make a drug. We are finding some interesting hits, as predicted, particularly against the targets which are more difficult to find leads. But there is an interesting example of a drug which is in early phase clinical trials for AIDS. It was not discovered as part of this program. It was part of the Kew Botanical Gardens Program in the UK. They were studying antifeedants—the sorts of agents that plants have in them to stop insects from attacking them. The plant was a mulberry tree. They discovered a compound in it called NJ, and by a chance discussion at a local British pub, it was decided to screen it for AIDS. It was found to be active. The chemists did some chemical work on this material and removed the toxic side effects, and it is an interesting compound that has made its way through the trials. That was about 1986.

The research which we have carried out has benefited Missouri Botanical Gardens. They are collecting their plants which is helping them compile the flora of North America.

What about the benefit of biodiversity to society as well? My argument is this; the more land that we can conserve for biodiversity, the greater our options to improve agricultural efficiency and to address environmental and health issues. The more effectively we learn to use its resources for agricultural production, the more land is made available for the conservation of biodiversity.

We must preserve and oper[illegible] this positive feedback loop if we are to meet the quality of life demanded by the world's population. Monsanto's research programs have a major interest in seeing that the correct balance is struck between conservation and the use of natural resources.

These programs will result in products which increase the health and welfare of the population by providing new medicines and an efficient agricultural basis essential for continued prosperity.

Thank you.

Mr. STUDDS. Thank you very much.

[The statement of Mr. Brewer can be found at the end of the hearing.]

Mr. STUDDS. Next, Dr. John Crossman of the Eastern Municipal Water District of San Jacinto, California.

STATEMENT OF DR. JOHN CROSSMAN, RESOURCE DEVELOPMENT ADMINISTRATOR, EASTERN MUNICIPAL WATER DISTRICT, SOUTHERN CALIFORNIA

Dr. CROSSMAN. Thank you.

Mr. Chairman, my name is John S. Crossman, and I am a Resource Development Administrator for Eastern Municipal Water District in Southern California. With me today is Mr. Rodger Siems, a member of our Board of Directors and a local farmer.

It is a pleasure for me to testify before the Environment and Natural Resources Subcommittee on EMWD's interest in and experience with plant species protected under the Endangered Species Act. However, before discussing our experiences, I would like to take a few moments to describe the Eastern Municipal Water District and the area we serve. Eastern is a public water district formed in 1950 under the Municipal Water District Act of California. Our service area is located in western Riverside County in Southern California. It is approximately 539 square miles and we serve approximately 400,000 people. The area is bounded on the east by the San Bernardino National Forest and the San Jacinto Mountains, on the north by San Bernardino County, on the south by San Diego County, and on the west by the Cleveland National Forest. We are a water district that is in transition. Historically our primary customer has been agriculture, but today the District is becoming a more suburban, residential area.

To meet the growing expectations of our changing customer base, EMWD has embarked on a $500 million capital improvement program over the next five years. Because of the uncertainty of imported water to our area, both in terms of cost and the availability, our Board of Directors has made the development, management and protection of local water supplies our district's highest priority. Stated another way, the Eastern Municipal Water District has made water conservation, water reclamation and reuse, and groundwater development and management its highest priority. These efforts have resulted in water projects that are at the cutting edge of responsible water resources management.

One of the challenges that we face in developing these projects is endangered species. By late 1992, the Federal Endangered Species Act protected over 1,000 plant and animal species in the United States, with 113 of those species found in California. These protections have resulted in approximately 144,000 acres, or 44 percent of our service area being designated as sensitive habitat for endangered species. With the recent addition of the California Orcutt Grass and the proposed listing of the San Jacinto Saltbush, this total is expected to increase even more. And, the list does not include any of the 159 plant species that are the subject of a public hearing in Willows, California, on November 10, 1993.

One of the District projects that was impacted by an endangered plant species was a seven-mile sewer line. The proposed alignment passed through a heavily disturbed area that had been zoned for industrial use in the City of Hemet's general plan. Eastern had prepared an environmental assessment for this project, and when no comments were received from the resource agencies or the general public, Eastern proceeded with construction in October of

1992. However, before we were able to get construction fully under way, new information became available from a biological survey by the Metropolitan Water District that indicated the possibility of sensitive species in the area.

Following this disclosure, the District immediately undertook a more detailed biological survey, and we found California Orcutt Grass. This finding was presented to the U.S. Fish and Wildlife Service and the California Department of Fish and Game to determine what was needed to resolve this issue. Unfortunately, after five months, we were unable to come to closure over what was needed and the District proceeded with a new alignment. This added approximately $530,000 to the total cost of the project.

The District also had a similar experience with the slender horned spineflower, another endangered species. This particular species was noted by a visiting professor from the University of California at Riverside, who was walking along one of Eastern's construction sites. During his walk he observed the emerging plant that had germinated as the result of fall rains. The alignment had been checked earlier and no species were noted at that time. Again, the ultimate solution was a new alignment to protect the endangered species.

These episodes represent some of the challenges Eastern Municipal Water District has been facing with endangered plant species. However, the impression I would like to leave the Committee with is how the District is dealing with endangered species in our area. We have embarked on a program that incorporates wetlands as part of our total water resource management program, which subsequently can create critical habitat for endangered species. We are also promoting the development of a multipurpose corridor that will link the national forests along our boundaries and serve as movement corridors for endangered species.

We appreciate the opportunity to appear before this Committee. We look forward to responding to any questions the Members may have.

Mr. STUDDS. Thank you very much.

[The statement of Dr. Crossman can be found at the end of the hearing.]

Mr. STUDDS. Our final witness is Dr. Linda R. McMahan of The Berry Botanic Garden, Portland, Oregon.

STATEMENT OF DR. LINDA R. McMAHAN, EXECUTIVE DIRECTOR, THE BERRY BOTANIC GARDEN, PORTLAND, OREGON

Ms. MCMAHAN. Thank you. I am Executive Director of The Berry Botanic Garden, which you probably never heard of. I hold graduate degrees in botany and law, and have studied how endangered plant laws have been passed and implemented, primarily in the States, and a little bit about the Endangered Species Act. Conservation of our Nation's plants and other natural resources is an important issue to me. In this regard, I chair the Conservation Committee of the American Association of Botanical Gardens and Arboreta. I am also honored to serve as a member of Oregon's Environmental Quality Commission, which oversees the activities of the Department of Environmental Quality in that State.

The first point I would like to make today is that botanical gardens all over the country and all over the world are very active in plant conservation efforts. We have heard already from Monsanto about the efforts of the Missouri Botanical Gardens and Kew Gardens and others in working toward some kind of conservation effort.

I would like to say that small gardens can do the same thing. I am from an institution that has an annual budget of $300,000, which by Federal standards is pretty low. We have a staff of 10, and yet we were the first botanical garden in the country to set up a regional seed bank for rare and endangered plants. That happened in 1983.

We work cooperatively with a number of Federal agencies. It is an essential kind of activity for our garden. We are working on nine different projects currently involving the Fish and Wildlife Service or the U.S. Forest Service and the Bureau of Land Management.

One of the plants we are going to be working on more extensively next year you see up on the wall, the western lily. That is one of the species that we work with in a number of different conservation activities. So with a relatively modest investment, by pairing our efforts with the Federal agencies, all made possible through the Endangered Species Act, we have been able to accomplish quite a deal already.

The second point is that the States of this Nation have made significant efforts on their own to conserve endangered plant species. Over half of them, 26 right now, have an endangered plant law in which there is protection similar to the Endangered Species Act. Another group has laws that help specifically in the conservation of those plants.

It is important that the Endangered Species Act now and in the future encourages and rewards the activities of the States that have their own programs, programs for conserving the plants, sometimes plants at the edge of their ranges, as Dr. Eisner referred to earlier, that are very important resources within those States.

Third, I would like to address the topic of this particular hearing today which is the medicinal use of plants. That is something that I have been interested in for some time. I estimate, based on some work that I have done in the past, that about half—probably more than half—of the rare and endangered plants in this country are related to plants that have been used medicinally by Native Americans or, in other uses, are used medicinally around the world; and just right off the top, have a very strong potential value for humankind.

For this hearing, I took a list that I had developed for other purposes. It is a list of 556 species, a combined list of rare and endangered plants from Idaho, Oregon and Washington. Just using 10 references that I happened to have in my office, in cross-referencing to the genre of those species, I found right around 50 percent that were related to plants that I could reference easily as having some kind of medicinal value. So I cannot say strongly enough just how important they are as a resource.

This is not really surprising. Plants have been evolving for thousands of years on their own. They have had a lot of stresses to deal

with in their lives. They are attacked by insects, they are eaten by various creatures. They have to compete with other plants around them.

What they have done is to create chemicals. They have created thousands and thousands of chemicals which serve those plants, to compete. They are tiny chemical factories.

Many of the new chemicals that we have heard about today have come from recent plant discoveries. I believe there are many more of these, and I believe that it is really important for us to recognize that and conserve that resource in any way we can. I think the Endangered Species Act has a lot of potential for doing that.

I thank you very much for allowing me to come here today.

Mr. STUDDS. Thank you very much.

[The statement of Ms. McMahan can be found at the end of the hearing.]

Mr. STUDDS. This is a remarkable panel. I really appreciate your time.

Let me observe at the outset that we may find our time limited because of events on the Floor which will call us away. As you probably all know, and if you don't know you should, the fundamental statute of the Endangered Species Act is in serious trouble here.

Some of you may have observed the debate on the Floor during the National Biological Survey authorizing legislation a few weeks ago. It engendered and elicited extraordinary amounts of emotion on the face of it far beyond anything to be justified by the relatively modest provisions of the National Biological Survey legislation. That is just a hint of the emotion to come, if and when we put on that Floor the Endangered Species Act or any other major environmental statute—Clean Water Act, Wetlands Provisions, et cetera.

Just in case the time runs out without my having been able to say this, I would just like to begin with a plea to each of you from whatever segment of the country you come, both professionally and geographically, if this subject is as important as you say it is—and I happen to agree with you that it is—it behooves each of us in our own way to convey that to those who speak for us and represent us.

Absent some extraordinary countervailing pressures to do the right thing here, we are quite likely to do other than the right thing when push comes to shove.

It is a challenge for those of you whose perspective is as yours, to convey that to Members of Congress who don't always have the luxury of taking the longer view and the greater perspective, to put it politely. So please think of that as a plea and as a charge.

I notice the gentleman from North Carolina is gone. If he were here, I know he would ask something like this. These are some of the quandaries that we face here.

Supposing someone has owned a piece of land for a great many years and is planning to subdivide it in his retirement years to produce income for his kids' college education or maybe his own retirement. Supposing we discovered, just as he is about to sell some of that property which he has held and planned for a lifetime for his own benefit and that of his children, that the last remaining population of an endangered plant which is very promising as a

cure for cancer perhaps is found and would be destroyed if that land were developed? What do we do?

How can we be fair to both the landowner himself who has in good faith provided responsibly for himself and his family's future, and how do we act in a way that is fair to the rest of mankind? That is a more polite phrasing or milder version than you might have heard. Does anybody have any ideas?

Ms. McMahan. To me, it is a very complex issue. It is more difficult for you than it is for me. My answer for myself is pretty easy, but that is not the political reality of today.

I think it is important to remember that we restrict private property rights for a very large number of reasons in this country. We restrict private property rights for purposes of the environment, wetlands and other things, we restrict property rights for preserving agricultural land, for cultural heritage, for public safety and for a lot of things.

I don't think that the question is a whole lot different when we talk about the issue of endangered plants than any other issue that we think is real important.

It is a difficult question. It is a difficult set of compromises, but I think it is something we have to address with the same fervor and the same belief in plants as a public good as we do those other things that we accept as a public good.

Mr. Studds. Do you think you could get every garden club in America to convey that to their representatives?

Ms. McMahan. I think that garden clubs are perhaps the easiest, sir. The Garden Club of America, which represents a great many garden clubs in this country, is very interested in this topic and very supportive of rights for endangered plants.

Mr. Studds. I hope they will let that be widely known in all 50 States.

Dr. Grever, you were speaking about the number of HIV-specific things. You noted that in several cases tropical substances have been isolated for preclinical development. How far are we from phase-one clinical trials in any of those situations?

Dr. Grever. One of the agents that is very interesting because it has a broad spectrum of activity against both HIV-1 and HIV-2 is called Michellamine B. It is currently undergoing toxicologic evaluation. Our hope is that this will enter a phase-one clinical trial within the first quarter of 1994. That is probably the closest one.

Mr. Studds. The October issue of the Far East Economic Review reports that trichosanthin, a compound derived from the root of a cucumber-like plant in China, shows promise. It says that 12 people with critical stages of the disease have used it with apparently total success. Do you know anything about that compound?

Dr. Grever. I cannot comment specifically. I have read something similar to that recently. This material has been submitted to our screen for *in vitro* evaluation.

Mr. Studds. NCI is investigating that?

Dr. Grever. Yes. I would have to go back and look at the data before I could comment specifically.

Mr. Studds. I would appreciate it if you could do that for us. Thank you.

[The information can be found at the end of the hearing.]

Mr. STUDDS. The gentleman from New York.

Mr. HOCHBRUECKNER. Dr. Eisner, in your testimony, you talked about gene flux. Could you explain that for all of us and give us a few examples?

Mr. EISNER. The terms that are being used currently are gene flux or horizontal gene transfer. The idea is genetic transfer, not from parent to offspring, but between species. I will give you an example from work done at Texas A&M.

There are tiny little parasitic wasps which lay their eggs in caterpillars. The eggs hatch and the little baby wasps eventually come out of the dead caterpillar. For these wasps to develop, they have to knock out the immune system of the caterpillar. They use a virus to do that. The virus also lives in the caterpillar and the wasp and the virus divide up the caterpillar's resources for their own benefit.

Studies were done to investigate how the immune system of the caterpillar is knocked out. That has been unraveled biochemically. Now some wasps have been found that knock out the immune system of the host in the same way but have no free living viruses associated with them. The most logical explanation is that the virus has been incorporated into the genome of the wasp. The wasp and the virus have become symbionts, and coupled in such a way that they are for all intents and purposes one and the same organism.

Another example: there are some compounds called trichothecenes. These are highly complex molecules which if one finds them in nature, one suspects a fungal source. They have been found by investigators from the University of Maryland in the leaves of certain composite plants of the genus *Baccharus.*

If you find that kind of compound in the leaf of a plant you say there must be a fungus there somewhere producing it for the plant. Indeed, they looked at the roots of the plant and found a fungus associated with the roots.

Now they find species of *Baccharus* that produce trichothecenes but apparently without a fungus. The most logical explanation is that sometime in recent evolution the genes of the fungus have been incorporated into the plant.

What this means is that gene transfer from one specimen to another occurs not only under experimental conditions in the laboratory but in nature.

What it tells us further is that by studying the interaction of organisms in nature we have things to learn that we have so far not even been able to imagine.

It means further that we need to take the long-range view when we are assessing the value of species. Species have "hidden value" that we are often not able to assess on the basis of knowledge now available to us.

Mr. HOCHBRUECKNER. On your first example, is there any evidence along this line with regard to the white wasp with its use in attacking the Lyme disease-carrying tick?

Mr. EISNER. I cannot respond specifically to your question because I am unfamiliar with that particular wasp as an agent of biological control.

Mr. HOCHBRUECKNER. Thank you.

Mr. STUDDS. The gentlewoman from Oregon.

Ms. FURSE. First, I would like to welcome Dr. McMahan from Portland. Certainly you are well known and your institution is also.

The question I would like to ask you is, since we don't know how many endangered plants there are, how about a worldwide register? Is there anything that you can use on a global level?

Ms. MCMAHAN. I have not looked worldwide. There are some efforts to do that. There are worldwide agencies, particularly the International Union for the Conservation of Nature, which keep a register of endangered plants around the world. The numbers are very high. I cannot speak to that.

Someone estimated around the world perhaps 50,000 plants that are known now to be at risk of extinction. I may be off, but the number is very, very high.

There has been some effort to look into the medicinal value; whenever you look at the potential medicinal value of a target list, it is always high. That simply reflects nature where the medicinal value is very high.

The problem, of course, is that we are dealing with up to perhaps 20 percent of the world's flora, including flora in this Nation, whether that be Hawaii which is a little higher or Michigan or Ohio. The 20- to 50-percent range is what we find for endangered plants.

This reflects the value of these plants, the fact that all plants have these chemicals that are useful. It is hard to come up with numbers.

Certainly, other people are looking at it. Certainly, they are very important.

Mr. STUDDS. I want to express again both my appreciation to you all and my regrets that the noise you hear up here is summoning us to the Floor. So we must leave this matter of cosmic consequence to vote on something of absolutely no significance whatsoever.

It is sort of the paradigm of our existence here. Some of you have the luxury to go back to your respective lairs and think. That is a process about which we have heard but have not participated in recently.

I want to thank you for a very sobering and very humbling hour. While you will go back, as I say, to your respective professions, we will at least have, for the remainder of the year, to remind us of what you have said, these extraordinary photographs on the wall.

I hope that they will serve that purpose. I also hope, as I said before, and I mean this very, very seriously, that each of you who have very different professional associations and very different regional associations and personal ones, will utilize whatever ones you have to try to convey the gist of what you are saying.

Dr. Eisner, I understand what you were saying. You have no choice. No thoughtful human being has any choice other than to look at the larger picture and the longer run here. It is an intellectual and perhaps even a moral imperative.

That does not, however, make any easier the immediate political chore that has to be accomplished in order to allow us to do this as

a nation. Presumably, we have to reauthorize and extend the statute in the face of some rather heated emotional controversy.

To the extent that we can focus people here on the larger questions which you have all raised so eloquently, each in your own way, we will all be far better off for it.

I thank you for your time and patience. I hate to ask you to do anything even remotely political, but in this case I think it will serve the interest of what brought us here together. Thank you very much. The Subcommittee stands adjourned.

[The statement of Mr. Fields follows:]

STATEMENT OF HON. JACK FIELDS, A U.S. REPRESENTATIVE FROM TEXAS, AND RANKING MINORITY MEMBER, COMMITTEE ON MERCHANT MARINE AND FISHERIES

Mr. Chairman, I appreciate your holding this hearing to further evaluate the medicinal use of plants and the protections they are afforded under the Endangered Species Act.

Using plants to treat wounds and diseases dates back thousands of years in human history. According to World Health Organization statistics, plant-based medicines play an essential role in the primary health care of 80 percent of the world's population. Approximately 25 percent of drugs currently prescribed in the United States contain at least one compound originally derived from plant material, including aspirin, oral contraceptives, cortisone, digitalis, and taxol. Research suggests that several plant compounds may also prove promising for the treatment of AIDS.

Although more than 250,000 plant species are known to exist on the planet, only a small fraction of these species has been examined for medicinal application. Regrettably, there is increasing concern that many species may disappear due to habitat destruction before their medicinal values can be discovered.

The Center for Plant Conservation (CPC) estimates that more than 200 plant species have become extinct in the United States alone. This century has seen the world's tropical rain forests, ecosystems known to contain more than half of the world's known plant species, decline from 16 percent to 7 percent of the earth's surface.

A striking example of these threats to medicinal research occurred two years ago in Malaysia when material from a tree was found to contain a compound (Calanolide A) which, in laboratory tests, had proven 100 percent effective in preventing the replication of HIV-1 (the AIDS virus). However, scientists were unable to retrieve additional material for testing due to destruction of the habitat. Fortunately, an additional search was initiated in the area and a tree with similar characteristics was finally located in 1992.

Although the ESA is intended to protect plants as well as animals, the extent of protection afforded to plants has been less effective than for other species. Many useful plants are being threatened by a loss of habitat, the introduction of exotic species, and the collection of plants for personal and commercial gain.

This hearing will give us the opportunity to review the success of the programs under current law, explore options for future protection, and discuss the impact of such protections on the private sector. As we do this, I would hope that we will keep in mind that limitations on land and land use have direct impacts on private property owners. While I support the goal of preserving plant species, it is important to consider all implications of such preservation, and make sure it is done in a reasonable way.

I look forward to hearing from the witnesses and learning more about the treatment of plants under the Endangered Species Act.

Thank you, Mr. Chairman.

[Whereupon, at 11:15 a.m., the Subcommittee was adjourned, and the following was submitted for the record:]

RELEASE UPON DELIVERY

TESTIMONY OF
Dr. Michael R. Grever

Associate Director
Developmental Therapeutics Program
Division of Cancer Treatment
National Cancer Institute
National Institutes of Health
Department of Health and Human Services

DRUG DISCOVERY AND DEVELOPMENT FROM NATURAL SOURCES: THE NATIONAL CANCER INSTITUTE EXPERIENCE

before the
Subcommittee on Environment and Natural Resources
House Committee on Merchant Marine and Fisheries
Rep. Gerry Studds, Chairman

NOVEMBER 9, 1993

Statement of Dr. Michael Grever
National Cancer Institute

Good morning, Mr. Chairman, and Members of the Committee. I am Dr. Michael Grever, Associate Director for the Developmental Therapeutics Program (DTP) of the National Cancer Institutes's (NCI) Division of Cancer Treatment, at the National Institutes of Health (NIH). With me today is Dr. Gordon Cragg, Chief of DTP's Natural Products Branch, and Dr. Francesca Grifo, a Program Manager in the International Studies Branch of the Fogarty International Center (FIC). Thank you for the opportunity to appear before you today to discuss the NCI's efforts to locate and develop medicinal compounds from plants to combat cancer and HIV (human immunodeficiency virus) infection and its sequelae. NCI is exploring and supporting a broad spectrum of ways to combat these two diseases, from prevention and diagnosis through treatment to rehabilitation and psychosocial care of patients. Drug development from natural products is just one avenue of emphasis; but until we can completely prevent cancer or HIV infection from occurring, it is an extremely important part of our effort to develop and design more effective and less toxic treatments.

In 1993, over 1 million new cases of cancer will be diagnosed in the United States and about 526,000 people will die of the disease. Since cancer incidence increases with age, most cases occur in adults at mid-life or older. There has been a steady rise in the cancer mortality rate in the United States in the last 50 years, with the major causes of this increase being lung, prostate, and breast cancers. The impact of cancer in general on minority and underserved populations is disproportionately great.

AIDS (acquired immune deficiency syndrome) was recognized as a distinctive syndrome over ten years ago and since then NCI has been involved in multiple disciplines of AIDS research. AIDS is not the primary mission of NCI; however, NCI leads the NIH's efforts in pediatric AIDS clinical studies, making advances in the identification and evaluation of potential therapies for HIV-infected children. Similarly, NCI heads efforts to develop therapies for HIV-associated malignancies, and has developed an extensive and comprehensive program to design and develop anti-HIV drug therapies. Following the discovery of the antiviral action of AZT (azidothymidine), ddi (dideoxyinosine), and ddc (dideoxycytidine) in the intramural NCI in the mid-1980's, the cancer drug screen was adapted for anti-HIV drug screening.

For our natural products drug screening effort to be at all successful, we must have available to us a multitude of species to study, and preservation of the species is critical to this effort. Global consumption patterns, perverse policy incentives and population pressures threaten biodiversity worldwide. In the countryside, exploitative resource management practices deplete soil and contaminate water supplies; deforestation for farming, pasture and building material leads to erosion and heavy flooding. The resulting disappearance of natural habitats has profound economic, environmental and scientific consequences. Among the ultimate consequences will be a loss of raw materials from which medicinal products might be developed.

BACKGROUND

Throughout the ages humans have looked to nature as a source of medicines for the treatment of a wide variety of diseases. Plants have formed the basis for sophisticated systems of traditional medicine, which have been in existence for thousands of years throughout the globe. Microorganisms and marine organisms have, however, played lesser roles in such traditional systems.

Natural products also play an essential role in the health care systems of developed countries, in providing new types of biologically active substances that either cannot be made chemically or would not have been conceived by chemists. Well-known examples of plant-derived medicinal agents include the antimalarial drug quinine, the analgesics codeine and morphine, the tranquilizer reserpine, and the cardiac glycoside, digitalis. The role of microbial fermentations has been predominant in the development of antibiotics, with over 8,500 substances isolated from microbial sources, and close to 100,000 prepared by chemical modification of the native material. Well-known classes of antibiotics are the penicillins, cephalosporins, and tetracyclines, while other microbial products include immunosuppressive, antiparasitic, and antifungal agents. Until the development of SCUBA (Self-Contained Underwater Breathing Apparatus), the exploration of the marine environment was virtually impossible, with the result that few marine natural products of medicinal value have been developed to date. That, however, is changing rapidly, and more thorough investigation of this area is yielding an increasing number of novel active substances.

NCI's NATURAL PRODUCTS PROGRAM: 1955-1980

Plants have a long history of use in the treatment of cancer, though many of the early claims for the efficacy of such treatments might be viewed with some skepticism since cancer, as a specific disease entity, is likely to be poorly defined in terms of folklore and traditional medicine. The NCI, however, recognized the potential value of plants and other natural materials as sources of new anticancer agents when it established its Cancer Chemotherapy National Service Center (CCNSC) in 1955. The aim of CCNSC was to coordinate a national program for the procurement and screening of materials for chemotherapeutic activity, and to develop and evaluate any active agents as potential drugs for the treatment of cancer. All materials, including synthetic compounds, purified natural products, and extracts, were screened against a range of animal tumor systems, principally experimental mouse leukemias. Bioassay-guided fractionation of active extracts led to the isolation and characterization of a large number of active agents belonging to a wide variety of chemical classes.

Extensive involvement of the pharmaceutical industry, either through contracts or voluntary submissions, provided over 180,000 microbial extracts from soil during this period, which yielded a number of active anticancer agents. Commercially available drugs from microbial origins that evolved through NCI efforts, as well as those developed by industry, include doxorubicin (adriamycin), mitomycin C, bleomycin, streptozotocin, L-asparaginase, and

mithramycin. During the same period, some 35,000 plant samples were collected from mainly temperate regions in over 60 countries, including the United States, through a collaborative agreement between NCI and the United States Department of Agriculture (USDA), and yielded over 114,000 extracts. Clinically active agents which have been developed through this program include Taxol® from the Pacific yew and other related species, topotecan and CPT-11, semisynthetic derivatives of camptothecin from a tree native to China, and homoharringtonine from another Chinese tree. In addition to Taxol® (whose initial *in vitro* activity was first observed in 1964 through the early program), which was approved by the Food and Drug Administration (FDA) in December 1992 for the treatment of patients with ovarian cancer, commercially available plant-derived anticancer drugs include the Vinca alkaloids vinblastine and vincristine, from the Madagascar periwinkle, and etoposide and teniposide, semisynthetic derivatives of epipodophyllotoxin, an analog of podophyllotoxin from the mayapple. The thorough investigation of marine organisms as sources of antitumor agents only started in the mid-1970s, but by 1981 over 16,000 extracts derived from 561 species representing 413 genera had been screened. Thus far, two marine organism-derived agents, didemnin B and bryostatin 1, have advanced to clinical trials, and the latter has shown promising early results.

NCI NATURAL PRODUCTS ACQUISITION PROGRAM: 1986-PRESENT

Despite the number of natural product-derived agents in clinical use or development, the NCI natural products discovery and development program was discontinued in the early 1980s, since it was perceived that few novel active leads were being isolated from natural sources. Of particular concern was the failure to yield agents effective against the major human solid tumors (breast, lung, colon). This apparent failure may have been due more to the limitations of the primary mouse screens rather than a deficiency of nature, and, beginning in 1985, a new *in vitro* screening strategy involving the use of 60 human tumors growing in cell culture was developed. This led to the implementation of new natural products acquisition, extraction, and isolation projects; further impetus and resources for these projects were provided by the initiation of a major new program within NCI in 1987 for the discovery and development of agents for the treatment of HIV-infection and its sequelae.

Contracts for the cultivation and extraction of fungi and cyanobacteria from international sources were established in 1985 and 1986, respectively; later contracts have focussed on the investigation of marine bacteria and simple animals. Marine organism collections have centered on the Indo-Pacific region since 1986, and collection contractors have included the Australian Institute of Marine Science, Harbor Branch Oceanographic Institute in Florida, and the Coral Reef Research Foundation based in Chuuk (TRUK Islands, Federated States of Micronesia). Contracts for the collection of plants from tropical and subtropical regions of Africa and Madagascar, Central and South America, and Southeast Asia were awarded to Missouri Botanical Garden, New York Botanical Garden, and the University of Illinois at Chicago (UIC) (assisted by the Arnold Arboretum at Harvard University and the Bishop

Museum in Honolulu), respectively, in 1986, and were renewed for a further five years in 1991.

In the microbial cultivation contracts, major use has been made of cultures from established collections, such as the American Type Culture Collection. Marine collections have been performed in the territorial waters of a number of countries, including Australia, Federated States of Micronesia, New Zealand, Papua New Guinea, Philippines and Thailand. Plant collections in Africa have been carried out in Cameroon, Central African Republic, Gabon, Ghana, Madagascar, and Tanzania. In Central and South America, plant collections have focussed on Belize, Bolivia, Colombia, Dominica, Dominican Republic, Guatemala, Honduras, Martinique, Paraguay, Peru, and Puerto Rico, while in Southeast Asia, collections have been performed in Indonesia (through the Arnold Arboretum), Malaysia, Nepal, Papua New Guinea (through the Bishop Museum), Philippines, Taiwan and Thailand.

DRUG DISCOVERY AND DEVELOPMENT

Dried plant samples and frozen marine macro-organisms are delivered to the Natural Products Repository (NPR) at the Frederick Cancer Research and Development Center (FCRDC), where they are stored frozen. Aqueous and organic solvent extracts are made by the Extraction and Grinding Laboratory at FCRDC, and are also stored frozen at the NPR, as are microbial extracts and microbial culture samples. Extracts are tested *in vitro* for potential antitumor activity against the panel of human cancer cell lines representing major disease-types, such as breast, colon, lung, and melanoma. As mentioned earlier, the screen currently comprises 60 cell lines. Anti-HIV testing is performed *in vitro* against a single human lymphoblastoid cell line infected with the AIDS virus. The NPR, extraction and screening laboratories are operated in NCI facilities at FCRDC by a contractor, Program Resources, Inc.

Active extracts are purified by NCI chemists using bioassay-guided fractionation. In bioassay-guided fractionation, all fractions produced at each stage of the separation procedure are tested for activity in the relevant bioassay, and subsequent fractionation steps are only performed on those fractions showing significant activity. This process of fractionation and testing is continued until the pure active constituent(s) is isolated. Bioassay-guided fractionation is essential since, in most instances, the active constituents are present in only small amounts in the crude extracts, and are generally isolated in yields of .01 percent or less, based on the mass of material. After the active constituent is isolated from an extract, its complete chemical structure is elucidated using modern spectroscopic techniques, and, if necessary and possible, x-ray crystallography. This isolation and structural elucidation of a potential new agent is but the first phase in a lengthy process of development towards clinical trials, and possible general clinical use. At any one time the total number of compounds being pursued at this stage for anti-HIV and anti-cancer activities is between 50-75.

Agents showing significant activity in the primary *in vitro* human cancer cell line or anti-HIV screens are entered into various stages of preclinical development to determine their suitability

for eventual advancement to clinical trials with human patients. The various stages of preclinical development are:

1. Large-scale production of the active agents through large-scale recollections of the source raw material from the original site of collection, or through cultivation of plants or aquaculture of marine organisms.
2. Formulation studies to develop suitable vehicles to solubilize the drug to enable administration to patients.
3. Pharmacological evaluation involving the study of various drug parameters (bioavailability in blood and plasma, rates and routes of clearance, and metabolism) in suitable animal models.
4. Toxicological evaluation of the drug to determine the type and degree of major toxicities in animal (rodents, dogs) models and safe starting doses for clinical trials in humans.

On completion of preclinical studies and favorable review by the NCI staff, all the necessary data are collated and submitted to the FDA as an Investigational New Drug Application (INDA). Once the FDA has approved an INDA, the various phases of clinical development may begin. Initial studies, also known as Phase I trials, are conducted in patients to determine the maximum tolerated dose of the drug in humans, and to observe the sites and reversibility of toxic effects. Once the maximum tolerated dose has been determined, and NCI staff are satisfied that no insurmountable problems exist with toxicities, the drug advances to Phase II clinical trials which are conducted to test the efficacy of the drug in patients with a range of different types of cancer or those with HIV infection and its sequelae. For drugs demonstrating beneficial effects in the Phase II trials, Phase III clinical trials are conducted against those disease-types responding to the new drug treatment, and the efficacy of the drug is compared with that of the best chemotherapeutic agents currently available. In addition, the new drug may be tried in combination with other effective agents to determine if the efficacy of the combined regimen exceeds that of the individual drugs used alone.

Since the NCI does not market drugs, collaborations with pharmaceutical companies are developed at the stage of human clinical evaluation and, if possible, even earlier in development. Once sufficient evidence has been accumulated, frequently by both the company and NCI, indicating that the new drug is effective for a particular disease, all the necessary information is assembled and the company then files a New Drug Application (NDA) with the FDA. The NDA generally will apply only to the particular responsive disease-type, and approval by the FDA usually permits marketing of the drug only for use in the treatment of that disease-type.

Since the passage of the Stevenson-Wydler Technology Innovation Act of 1980 and the Federal Technology Transfer Act of 1986, it is a national policy to transfer federally-owned or originated technology to the private sector whenever appropriate. The Act also encouraged, as a national policy, joint research and development projects between

government laboratories and industry. Indeed, these are duties of each laboratory. NCI has followed the policy of seeking partners in private industry to commercialize its discoveries an inventions. The purpose of our Cooperative Research and Development Agreement (CRADA) with pharmaceutical companies is to conduct collaborative research on the development of drugs and to generate data necessary to obtain FDA approval of the compound. CRADAs are awarded following full and open competition, including publication in the Federal Register, and a thorough scientific review by government scientists of the proposals submitted. Prior to the award of a CRADA, a company must show it is the most qualified to undertake a potentially complicated and expensive effort to produce the agent and to cooperate with NCI in performing necessary clinical trials. In exchange, NCI agrees to provide the company with exclusive access to its clinical and preclinical data for use in obtaining approval for the commercial marketing of the product. The same competitive procedures are followed in licensing NCI-owned patents.

RECENT NCI DISCOVERIES

A total of 54,000 extracts, derived from all natural product sources, have been submitted for anti-HIV screening since about 1986. To date, over 35,000 plant samples have been collected by the NCI contractors, and over 25,000 have been extracted to yield more than 50,000 plant extracts. Over 25,000 of these plant extracts have been tested in the anti-HIV screen, and about 2,700 have exhibited some *in vitro* activity; of these, close to 2,400 are aqueous extracts, and in the majority of cases the activity has been attributed to the presence of ubiquitous types of chemicals, such as polysaccharides and tannins. Such compounds are not a current NCI focus for drug development and typically are eliminated early in the discovery process. Therefore, the number of extracts undergoing active investigation is much smaller.

A number of novel *in vitro* active anti-HIV agents have been isolated and selected for preclinical development. The dimeric alkaloid, michellamine B, has been isolated from the leaves of a tropical vine collected in the rainforest regions of southwestern Cameroon. Michellamine B shows *in vitro* activity against both the HIV-1 and HIV-2, and is in advanced preclinical development. Preliminary surveys of the occurrence and abundance of the species, as well as cultivation experiments, have been carried out by Missouri Botanical Garden through its contract with the NCI. Surveys thus far indicate that its range and abundance are very limited, but fallen leaves collected from the forest floor have been shown to contain reasonable quantities of michellamine B; the collection of these leaves has obviated the large-scale harvest of fresh leaves, and avoided possible endangerment of the wild species. Fallen leaf collections will provide sufficient michellamine B to complete preclinical studies, but the NCI is proceeding with feasibility studies of the cultivation of the plant through contract mechanisms. The collections and cultivation experiments are being performed with the full participation of Cameroon authorities and scientists, as well as through close collaboration with the World Wide Fund for Nature, which is coordinating conservation projects in the Korup region of Cameroon. Thus far, no other related species have shown significant anti-HIV activity.

Calanolide A is a novel coumarin isolated from the leaves and twigs of a tree collected in the rainforest regions of Sarawak, Malaysia. Calanolide A shows potent *in vitro* activity against HIV-1 and several resistant strains of the virus, but not against HIV-2, and is in early preclinical development. Recollections of plant material of the original plant species from the same general location have shown a range of test results varying from reasonable activity to total lack of activity. It is apparent that the production of calanolide A is dependent on various factors, possibly including the immediate growth environment and the time of harvest. Thus far, calanolide A has not been detected in any of the recollections, and the original source tree cannot be located. Careful taxonomic and chemotaxonomic studies of this species are being performed by the UIC, under contract to and in collaboration with the NCI and scientists from Sarawak. A survey of related species has shown that the latex of another species collected in the same region yields the related compound, costatolide, which has significant *in vitro* anti-HIV activity, though being somewhat less active than calanolide A. Costatolide and a derivative have also been approved for preclinical development. The latex contains high yields of costatolide, and would be an excellent renewable source of the compound, should it advance to clinical development. In addition, the synthesis of calanolide A has recently been reported.

A novel chemical compound, conocurvone, has been isolated from a plant species endemic to Western Australia; this plant was originally collected for the NCI program by the USDA in 1981. Conocurvone exhibits potent *in vitro* activity against HIV-1 and is in early preclinical development. Conocurvone has been synthesized from a simpler chemical which can also be isolated from the plant, and in addition, other simpler analogs have been synthesized and shown to possess equivalent *in vitro* anti-HIV activity. The development of conocurvone or related compounds will be undertaken in close collaboration with Australian scientists, and surveys of the occurrence and abundance of the source plant and related species are being carried out by the Western Australian Department of Conservation and Land Management.

Another potential anti-HIV agent, prostratin, has been isolated from the stemwood of a Western Samoan tree. This tree is used in Western Samoa for the treatment of a variety of diseases, including yellow fever, and an extract of the stemwood was provided by Dr. Paul Cox of Brigham Young University. While prostratin belongs to the phorbol class of compounds which frequently exhibit significant tumor promoting properties, it does not appear to be associated with tumor promotion, and has been selected for early preclinical development.

Of the approximately 30,000 extracts tested so far in the *in vitro* human cancer cell line screen, which started after the anti-HIV screen, a very small percentage (< 1.0 percent) have shown some degree of selective cytotoxicity. Interesting, novel patterns of differential cytotoxicity have been observed, and while some have been associated with known classes of compounds, others appear to be new leads which are being investigated further. Two natural products currently approved for preclinical development are halomon, isolated from a red algae collected in the Philippines, and halichondrin B, isolated from a species of marine

sponge found in the western pacific ocean. The procurement of materials for future development is underway.

NATIONAL COOPERATIVE DRUG DISCOVERY GROUPS

In addition to the direct NCI drug discovery and development efforts described above, the NCI established a number of National Cooperative Drug Discovery Groups in the mid-1980s, funded through competitively awarded cooperative agreements. The purpose of these groups is to carry out investigator-initiated research on the discovery of new anticancer agents utilizing approaches of their own design. In many cases, these groups include industry partners in order to move new agents rapidly to clinical trials and the market. Several of these groups are devoted to the exploration of natural products and thus represent another important approach to the development of agents from this invaluable source. In fact, one of the drugs mentioned earlier, topotecan, arose from that program.

ISSUES OF INTERNATIONAL COLLABORATION AND COMPENSATION

The current NCI collections are being carried out in over 25 countries situated mainly in tropical and subtropical regions. Recognition of the value of the natural resources (plant, marine and microbial) being investigated by the NCI, and the significant contributions being made by the source country's local scientists and traditional healers in aiding the performance of the NCI collection programs, has led the NCI to formulate policies aimed at collaboration with, and compensation of, countries participating in the NCI drug discovery program. The Letter of Collection (LOC) (formerly known as the Letter of Intent) formulated by the NCI contains both short-term and long-term measures aimed at assuring source countries of NCI's intentions to deal with them in a fair and equitable manner. The LOC forms the basis for agreements between the NCI and source countries, usually represented by organizations such as botanical institutions, pharmaceutical research institutes, universities, or appropriate government agencies. The NCI has signed agreements (based on the LOC) with organizations in eight countries (Awa Federation in Ecuador, Cameroon, Gabon, Ghana, Madagascar, Philippines, Tanzania, and Zimbabwe), and agreements with a number of additional country organizations are being considered or negotiated.

In the short-term, NCI periodically invites scientists from source country organizations to visit the drug discovery facilities at the FCRDC to discuss the goals of the program and explore the scope for collaboration in the drug discovery effort. These visits invariably result in a better mutual understanding of the goals and concerns of each party, and expedite the initiation of collection programs. When laboratory space and resources permit, qualified scientists from source country organizations are invited to spend up to 12 months working with scientists in NCI facilities on the bioassay-guided isolation and structure determination of active agents, preferably from organisms collected in their countries. Scientists from nine countries (Australia, Cameroon, China, Israel, Korea, New Zealand, Philippines, Tanzania, and Zimbabwe) have carried out, or are presently undertaking, collaborative research projects with scientists in NCI facilities.

Concerning compensation issues, the NCI applies for patents on active agents isolated from plants and other organisms collected from source countries. Should an agent eventually be licensed to a pharmaceutical company for production and marketing, the NCI will require the successful licensee to negotiate and enter into an agreement with the appropriate organization or Government agency in the relevant source country. Such an agreement will address the concern of the source country that appropriate organizations, agencies, and/or persons receive royalties or other forms of compensation. The NCI will also require the successful licensee to seek as its first source of supply the natural products available from the original source country. This process is already underway for conocurvone; other compounds will follow suit as they reach the appropriate point in development.

POLICIES FOR DISTRIBUTION OF EXTRACTS TO ORGANIZATIONS OUTSIDE THE NCI: MATERIAL TRANSFER AGREEMENTS

The NCI Natural Products Repository represents an invaluable national resource for the discovery of potentially valuable drugs. A great deal of interest has been shown by other research organizations and companies in the screening of materials from the repository, utilizing different screens and approaches from those of the NCI. After consulting source country representatives, either directly or through their respective collection contractors, the NCI has formulated a policy for the distribution of extracts to carefully selected organizations. In applying for access to NPR materials, research organizations and individual investigators must submit research proposals which clearly delineate the research to be performed. The importance and relevance to the NCI mission, prior work in the area, the specific approach to be used, and the ability to carry out the research in a timely manner all need to be clearly defined in the proposals. Screening must be for activities against diseases related to the NCI mission (cancer, AIDS, opportunistic infections) or against diseases which have an impact on health in developing countries. The inclusion of diseases of major concern to developing countries is considered very important, since most of the countries participating in the NCI collection program are developing countries. Proposals are reviewed by a committee of senior NCI staff, and are judged primarily on their scientific merit and the relative importance of the proposed research. A key factor determining the selection of recipient organizations is the agreement by the organizations to abide by the same policies of compensation and raw material supply as stated in the LOC. Approval for distribution of extracts is granted only after the organization has signed a legally binding Material Transfer Agreement (MTA) with the NCI. The MTA contains a clause guaranteeing the rights of source countries to compensation in the event of production and marketing of a drug from an organism collected within their borders, and requiring the recipient to utilize the host (source) country as the first source of supply of raw material for production of the marketed agent.

DRUG DISCOVERY AND BIOLOGICAL DIVERSITY CONSERVATION

The NCI states in its LOC that "while investigating the potential of natural products in drug discovery and development, NCI wishes to promote the conservation of biological diversity."

While not being directly involved in the conservation of biological diversity, the NCI, through its extensive contract-supported collection programs, has provided support for research activities by source country botanists and botanical institutions in the expansion of inventories and herbarium holdings of their flora. The NCI collection program has also provided the stimulus for obtaining additional support from other organizations, such as the United States Agency for International Development (USAID), the World Wildlife Fund, and the National Geographic Society.

The International Cooperative Biodiversity Groups program

The purpose of the International Cooperative Biodiversity Groups (ICBG) Program is to address the interdependent issues of biodiversity conservation, sustained economic growth, and human health, in terms of drug discovery for diseases of concern to both developing and developed countries. The NIH's FIC serves as the organizational locus for this program, which involves joint participation with the NCI, the National Institute of Allergy and Infectious Diseases, the National Heart, Lung, and Blood Institute, the National Institute of Mental Health, the National Science Foundation, and the USAID. The unifying theme underlying this program is the belief that the discovery and development of pharmaceuticals from natural products can, under appropriate circumstances, promote sustained economic activity in developing countries while conserving the biological resources from which these products are derived.

The ICBG Program is a result of a workshop, sponsored by the three Federal agencies, held in 1991. This workshop brought together experts from developing countries, ethnobiologists, conservation biologists, representatives of the pharmaceutical industry, and legal experts on intellectual property rights.

The ICBG Program accomplishes its goal by linking developing country organizations and indigenous peoples with United States' academic and industry partners to develop and implement innovative strategies for the conservation and sustainable management of biological diversity. This occurs through economic returns from screening medicinal and other organisms for compounds active against both developing- and developed-country diseases, agricultural and veterinary purposes, and in some instances parallel development of medicinal or other products for host country markets.

ICBGs have active and substantial participation by United States and developing country scientists and institutions. A critical component of the activities is to ensure that equitable economic benefits from these discoveries accrue to the country of origin. This is accomplished through benefits sharing agreements drawn up among members of each ICBG. Group activities include, for example, implementation of strategies to support the selection and acquisition of natural resources and novel agents, including the use of ethnobiological studies and equitable collaborations with indigenous peoples; the preparation of crude materials for testing activity against relevant diseases; development of long-term ecological

and economic strategies to ensure the sustainable harvesting of targeted organisms; use of novel contractual or other legal mechanisms to ensure equitable distribution of potential financial rewards; incorporation of systematists, ecologists, and anthropologists in integrative surveys of a developing country's biological diversity; and production and documentation of all collected material in the form of published works, and/or databases, reporting specific locality and all features of biology relevant to standard botanical and zoological collections.

Programs assure accessibility of inventory data to all individuals, including those not associated with the ICBG, by housing catalogues and databases in public institutions (such as universities and national museums) and, when databases are kept on computer systems in private institutions, by including in publications specific references to these databases.

The ICBG program raises novel legal issues that link ordinarily distinct legal fields, such as environmental and intellectual property law. The principles were derived from the Request for Applications issued in November 1991 by NIH on behalf of the three Federal agencies funding the program. They are considered minimum standards for treatment of conventional intellectual property rights, plans for the distribution of benefits to developing countries, disclosure to and consent of indigenous or traditional sources, respect for indigenous concepts of intellectual property, balancing public access to and protection of proprietary information, compliance with environmental laws, and attention to issues of sustainability.

Thirty-four applications were receive and reviewed; three awards were made on September 30, 1993, for five years, and two other awards will be made in FY1994.

CONCLUSION

The number of potentially valuable drug development "leads" from plant and animal sources is likely to be only one in 5,000-10,000, and, based on our experience with drugs for cancer, the chances of discovering an effective commercial drug such as Taxol® are significantly less. In addition, the time span for development of a drug to commercial use has been as long as 10-20 years, although we hope to quicken that pace significantly. Accepting that the protection and maintenance of biodiversity must be capable of generating real economic benefits to the society providing these services, one might think that drug discovery and development (pharmaceutical prospecting) might not provide an economic incentive to justify conservation of biodiversity. However, the development of new screens and the dramatic improvements in screening technology, are significantly expanding the potential of natural products as sources of new drugs and other bioactive agents (e.g., agrochemicals). The emergence of increasing resistance of diseases, such as malaria, tuberculosis, and pneumonia to commonly-used drugs, and the scourge of the global AIDS pandemic, make the necessity to discover new drugs all the more urgent. While it is impossible to determine what percentage of species have been fully investigated for pharmaceutical potential, it is likely that the percentage is extremely small; some estimates place it at less than one percent.

Clearly, the exploration of plant species, as well as other sources of natural products, as sources of valuable pharmaceuticals for cancer, HIV-infection and its associated diseases, and other diseases, should be considered a high priority for active investigation. From a practical point of view, the preservation of these natural resources is critical. NCI has recognized this and made several important moves to ensure that scientific leads emanating from natural products can be pursued without exploiting the countries from which these products are taken.

NCI also recognizes the need for the public to be kept abreast of new developments in all aspects of cancer research, and has established a toll-free regional Cancer Information Service, **1-800-4-CANCER**, so that patients, their families, and their physicians can receive up-to-date information about their disease and its treatment. Information specialists are equipped to provide callers with details about all NCI-supported clinical trials testing new agents, including many of those mentioned here today. I should mention as well that the NIAID, the FDA, the National Library of Medicine, and the Centers for Disease Control and Prevention jointly support a toll-free AIDS clinical trials information service, which can be accessed by telephone; that number is **1-800-TRIALS-A**.

In conclusion, I can assure you that NCI is working to bring cancer and AIDS patients new diagnostic procedures and treatments to help eradicate, slow, or prevent the progress of their disease and to ease anxiety and suffering. In our laboratories at the NCI and in our many grantees' and contractors' laboratories across the country, we have the best assemblage of men and women in the scientific world. I would like to emphasize that we confirm our commitment to reduce death and suffering from cancer and AIDS and this commitment is made with a full awareness of this awesome challenge. We have no illusions that this is an easy task.

I would be pleased to answer any questions.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

JAN 18 1994

The Honorable Gerry Studds
Chairman, Subcommittee on Environment and Natural Resources
Committee on Merchant Marine and Fisheries
House of Representatives
Washington, DC 20515

Dear Mr. Studds:

Thank you for the opportunity to testify at the November 9 hearing on drug discovery and development from natural sources. As I stated at the hearing, the National Cancer Institute (NCI) is committed to bringing cancer and AIDS patients new diagnostic procedures and treatments to help eradicate, slow, or prevent the progress of their disease. The exploration of plant species and other natural products as sources of valuable pharmaceutical agents is considered by NCI to be a high priority for active investigation. At the same time, we recognize that the preservation of natural resources within the host country is critical to preserving both the resource and financial interest of the country of origin.

At the hearing you asked whether NCI was exploring a compound derived from the root of a cucumber-like plant from China, as a potential anti-HIV agent. At the time I could tell you that, while NCI had received quantities of "Compound Q" for screening, I did not know the outcome of those tests. Please allow me to take this opportunity to update you on the status of our research with this agent.

Compound Q, also known as trichosanthin, is a protein isolated from the plant Trichosanthes kirilowii. Several scientific papers have been published on this substance, covering a variety of subjects, including its possible utility as an anti-HIV agent and its other biological properties.

Since 1987, a number of samples of trichosanthin, as well as extracts of the plant itself, were obtained by NCI from a variety of sources in the U.S. and China. These materials were tested in the standard anti-HIV screen used to detect substances worthy of further development. None of these samples has demonstrated activity in this screen, and NCI has no plans at present to pursue trichosanthin as an anti-HIV agent. This decision is, of course, subject to further review and consideration by NCI based on additional scientific information, either preclinical or clinical, that may become available in the future.

Page 2 - The Honorable Gerry Studds

The National Institute of Allergy and Infectious Diseases (NIAID) AIDS Clinical Drug Development Committee considered the Genelabs formulation of trichosanthin, known as GLQ223, in February 1992. Based on available scientific data, they recommended that further clinical evaluation of GLQ223 not be supported by NIAID at that time.

I hope this answers your questions. Should you require further information please do not hesitate to call me at (301) 496-8721.

Sincerely,

Michael R. Grever, M.D.
Associate Director
Developmental Therapeutics Program

TESTIMONY OF DR STEPHEN J. BREWER TO THE SUBCOMMITTEE ON ENVIRONMENT AND NATURAL RESOURCES, NOVEMBER 9, 1993

SEARCH AND DISCOVERY OF PLANT DERIVED BIOACTIVE CHEMICALS AT MONSANTO-SEARLE

By: S.J. Brewer
Manager, Bioproducts Chemistry
Monsanto Corporate Research

Plant Derived Bioactive Chemicals

Introduction

Monsanto is a world wide development, manufacturing and marketing company of high value agricultural and chemical products, pharmaceuticals (Searle) and food ingredients (NutraSweet) with 1992 sales of $7.8 billion. Over the past four years Monsanto has collaborated with the Missouri Botanical Gardens to obtain approximately 10,000 plant samples from the United States and Puerto Rico. The rationale for and utility of this activity to Monsanto's ongoing drug and agrochemical discovery programs is described.

Nature has been, is, and will continue to be, a key source for the discovery of new products of value to humanity. The plants of the earth's ecosystems have proven to be mankind's medicine chests. Eighty percent of people in developing countries rely on medicines derived from plants (Farnsworth, 1990). These people generally have an intimate knowledge of their medicinal flora and exploit a wide variety of species. Drugs derived from plants are a major part of the pharmacopeia of western medicine as well, many adopted from traditional folk remedies. The early European botanical gardens were primarily collections of medicinal plants rather than display gardens. The plants then formed the basis of western medicine.

The importance of natural chemicals in the development of Western medicine can be illustrated by studying the evolution of the twenty best-selling drugs in the United States. This analysis demonstrates that most of these modern medicines (which accounted for six billion dollars in sales in 1988) have benefitted from natural products research. Plants had a key role to play in the development of seven of these twenty medicines, supplying either the medicines themselves, leads for medicinal chemists, or precursors for drug synthesis (Table 1). Of all of the medicines marketed in the United States, Farnsworth (1990) has estimated that 199 or about 25% contain active ingredients extracted from plants. The value of the medicines derived directly or indirectly from natural resources in 1984 was estimated at greater than 20 billion dollars (Farnsworth, 1984). The figures above indicate that directly or indirectly, the majority of western medicines owe their existence to natural products research.

Discovery of Modern Medicines

Advances in medicinal science during the last century led to the realization that specific chemical compounds are responsible for the effects of drugs. During this century research into the mode of action of these bioactive chemicals has shown that they have utility because they inhibit or stimulate specific target molecules (usually protein-based receptors or enzymes) in the diseased animal. In addition, the direct ancestors (leads) of today's top drugs were found by random screening or analogue synthesis and testing, or else by chance observation (Table 1).

Therefore, the modern rational approach to drug discovery uses our knowledge of disease states and biology to identify protein based targets which, when agonized or antagonized, are hypothesized to yield a useful medicinal effect. However, as the structure of such bioactive chemicals cannot be adequately predicted, large numbers of chemicals, either analogs of enzyme substrates or hormones (10^2-10^3) and/or randomly selected synthetic chemicals and extracts of natural products (10^3-10^6) are screened to yield the first generation of bioactive chemicals. These may yield products themselves, or the discovered structure/activity relationship becomes the basis for a synthetic chemical analogue program to reduce toxicity, improve biological activity and bioavailability.

Plants as Sources of New Medicines

Given the historical importance of plants as sources of medicines and these improved technologies, there has been a resurgence in interest in screening plants for pharmaceuticals. Plants are collected on the basis of random, taxonomic, and ethnobotanical information. Random collecting is based on evidence that genera within families often exhibited considerable chemical diversity, but species within a genus were likely to be chemically similar. Thus collecting in regions of high taxonomic diversity is likely to increase significantly the chemical diversity to be screened. Taxonomic collecting is based on the general tendency for related taxa to contain related compounds. This leads to two general applications of this method. First, when the source of a bioactive compound is known, screening related taxa may yield compounds of similar structure with greater efficacy or reduced toxicity. A second application of taxonomic collecting is to search for better sources of known compounds. Collecting guided by ethnobotanical data has been applied in two ways to drug discovery programs. One approach is the study of the uses of ~~various~~ plants in traditional medicine, followed by a testing of their true effectiveness in these applications. Positive results from this type of work depend upon careful disease recognition and precise documentation of uses of herbal remedies. The second approach has been random screening of plants used in traditional medicine based on the assumption that they have a higher probability of yielding bioactive compounds. The use of the ethnobotanical approach has the advantage of providing a 'prescreen' for bioactive compounds (Miller & Brewer, 1992).

Monsanto-Searle's Plant Screening Program

The challenge to the technologists using the random screening technique is to obtain a large and diverse collection of chemicals. The natural diversity found in plants is almost infinitely large because it is the product of the interplay of both genetic environmental factors. Therefore, over the past four years, Monsanto-Searle has collaborated with the Missouri Botanical Gardens in St Louis to obtain approximately 10,000 plant samples for use in both drug and agrochemical discovery programs using the random collection strategy. These samples have

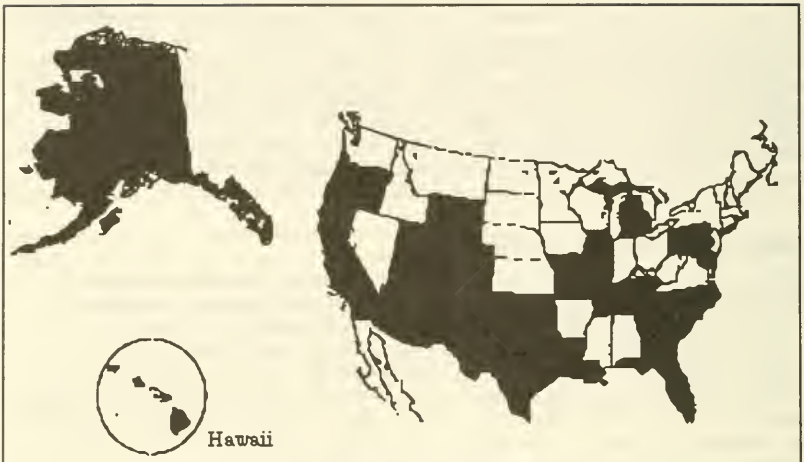

Figure 1 : Regions of the USA Sampled by the Missouri Botanical Gardens for Monsanto-Searle

been obtained by botanists from regions in the USA which are rich in plant biodiversity (Figure 1). They are collected from public, government and private land after obtaining the necessary authority and permits. Endangered species are identified before hand and are not collected. Samples are shipped to Monsanto, extracted and screened for the desired biological activity. The USA was chosen for this work because of its large resources of native plants growing in diverse environments, easy access and well documented flora. Over the past four years, Monsanto has spent over $1 million on sourcing plants for their screens and plans to continue the program.

The next challenge is to develop and supply the analytical technology to screen the collected plants in a reasonable time. Devising the screen to test large numbers of samples requires a major commitment and considerable analytical skill. Cell biology and biotechnology advances provide sufficient quantities of the protein based targets to support large scale random screens. High throughput screens are devised and results analyzed using microanalytical methods combined with computerized data handling. When a 'hit' is identified, advanced separations and structure elucidation methodologies are used for the isolation of natural product chemicals and the assignment of structure. In order to obtain sufficient

quantities for this work, recollection and taxonomic screening for higher yielding strains, or producers of chemical analogues may occur. It is usual for many plant extracts to be followed simultaneously with 'hits from other natural product sources such as microbes and marine organisms, as well as synthetic chemical libraries. All along the way, positive results in more advance biological models, identification in the literature for known chemicals produced by the plant and information about possible related ethnobotanical uses of a plant, keeps the necessary level of enthusiasm for following the 'hit'. In this way, an exciting and fast pace race is run until an extensive structure/ activity relationship is developed and a 'hit' becomes a 'lead compound'. At the same time, a plant extract will be tested in many other screens running in parallel, and a plant extract which fails in one screen may yield actives in another. Thus a plant can never be described as having no value. All this amounts to a multimillion dollar annual investment in which the plants are playing their predicted role in producing many useful hits and a number of promising novel structure/activity relationships.

Although it is too early to see how the plants will fair in this race for new medicines (it takes 10-15 years to get a new medicine to the market and only an estimated five out of 10,000 leads makes it to the market place), it should be noted that Searle is presently pursuing Butyl-DNJ, a potential AIDS medicine, through early phase clinical trials. The natural chemical, DNJ, was isolated from plant materials and shown active in *in-vitro* cell culture assays by a group working in Kew Gardens in the UK on insect antifeedants from mulberry trees. The native compound was too toxic to be useful, but after a number of analogues were then made and tested, and Butyl DNJ was made and shown to have the necessary properties to be advanced into the clinic.

Monsanto also has an agricultural discovery program which benefits from this project. Some of the samples shipped to Monsanto are extracted for proteins which are screened for the desired biological activity against plant diseases. Active proteins are purified, sequenced and the gene responsible for its production identified. This gene can then be cloned into plants to enhance the performance and productivity of crops which yield both food and materials. Extracts enriched in small chemicals are also screened for activity against crop diseases or weeds. Active chemicals from these extracts are isolated and their structures elucidated as described for human medicines.

This program has facilitated Missouri Botanical Garden's botanical collecting and specimen acquisition for North American plants. Each herbarium specimen is a modern record of species distribution, tying in with the efforts of the 'Flora of North America' project, coordinated by the Missouri Botanical Garden, to document the distribution of all species that exist in the United States, Canada and Greenland. This ultimately will provide some of the botanical data essential to the establishment of a National Biodiversity Survey.

Conclusion

It is essential that the described natural product discovery programs have access to reserves of biological diversity. The balance of how much land should be used to conserve biodiversity vs how much should be put to agricultural use is an issue facing policy makers. It should be noted, however, that provided the population is controlled, the more efficiently land is used for agricultural production, the more land is made available for the conservation of biodiversity. And the more land we can conserve for biodiversity, the greater are our options to improve agricultural efficiency and to address environmental and health issues. We must preserve and operate this 'positive feedback loop' if we are to meet the quality of life demanded by the world's population.

Monsanto's research programs have a major interest in seeing that the correct balance is struck between conservation and use of natural resources. Efforts are driven by the need to meet society's demands to provide an improved quality of life to an ever increasing population. These programs will result in products which increase the health and welfare of the population by providing new medicines and the efficient agricultural basis essential for continued prosperity.

Acknowledgement

I would like to acknowledge Dr J. Miller, of the Missouri Botanical Gardens for his useful help and discussions in the preparation of this manuscript.

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Table 1. Roles of natural products and screening in the development of the top selling U.S. medicines.

The top twenty best selling U.S.A. drugs with total sales approaching 6 billion dollars in 1988 (data supplied by IMS International) fall into 11 therapeutic classes. The role of natural products research in the development and understanding of these therapeutic classes and the role of screening in discovering the lead compound which resulted in these drugs, was abstracted mainly from the work of Sneader (1986); other general references were Gilman et al. (1990) and that for Mevacor from Vagelos (1991).

Natural products from exogenous sources (plants, microbes, and non-mammalian animal tissues) were involved in understanding the pharmacology of all therapeutic classes with the exception of female sex hormones, which were isolated from mammalian tissue. In eight of these therapeutic classes, the natural chemicals were used therapeutically as is, or as synthetic chemical derivatives, to treat human ailments at one stage in the development of the current medicines. Three of the classes still use naturally derived chemicals in their current products.

The role of screening in the development of these medicines was discerned by identifying how the lead compound (the direct bioactive chemical ancestor of a drug) was discovered. This analysis indicates that the twenty top selling drugs were developed from fourteen lead compounds. Random screening, where no significant structure preconditions were used to select the compound, resulted in seven of the fourteen leads. Analogue synthesis and testing, where structures of a hormone or an enzyme's substrate were used to synthesize analogues, resulted in the discovery of three of the fourteen lead compounds. Unexpected observations, whether in the clinic or during screening, were responsible for the discovery of three of the fourteen lead compounds. In the case of the female sex hormones, the lead compound was the natural biochemical itself. This is in contrast with the other leads which antagonize the activity of biological molecules.

Table 1 cont.....

Plant Derived Bioactive Chemicals

USE/ NAME	ROLE OF NATURAL PRODUCTS	ROUTE OF DISCOVERY
Adrenaline Antagonists Atenolol & Metoprolol	Ergot, a fungus which infected and poisoned wheat had been used medicinally since the middle ages. One isolated active alkaloid was ergotoxine. This had the new property of reversing (antagonizing) many of the actions of adrenaline, notably that of increasing blood pressure (1905).	In a screen for bronchodilators, dichloroisoprenaline was observed, to block adrenaline action (c1957). It was recognized that this unexpected activity could protect the hearts of patients with coronary disease from adrenaline released by physical or emotional stress. Medicinal chemistry of this lead increased the selectivity for heart receptors and reduced toxicity.
Anti-inflammatory Piroxicam, Sulinac & Naproxen	A glucose derivative of salicyclic acid (salicin) is produced by willows. These grow in cold damp places which is also conducive to rheumatic fever. Influenced by herbalist doctrines that antidotes are found in the vicinity of poisons, salicyclic acid was tested in patients as an antirheumatic, and shown to have beneficial effects (1874).	Piroxicam was the product of extensive chemical programs to overcome the toxicity of salicyclic acid. Other leads were found by screening in an animal inflammatory model. Sulinac was developed from an idomethacin lead discovered by testing serotonin analogs (c1963) and the phenoxyalkanoic acid lead for Naproxen was found (c 1962) by random screen of chemicals (originally a herbicide). Medicinal chemistry reduced toxic effects.
Antianginals Diltiazem & Nifedipine	The first antianginals were organo nitriles of glycerol and amyl alcohol which were shown to dilated blood vessels (1865). Clinical tests showed that these compounds could treat angina. Glycerol and amyl alcohol were both natural products isolated respectively from the manufacture of soap, from animal fats and alcohol, from yeast fermentation.	In a routine animal screen, analogs of dihydropyridine were shown to cause a relatively long lasting drop in the blood pressure of dogs (1965). This was shown to be due to coronary vasodilating activity. An extensive medicinal chemistry program improved the oral activity of this lead
Antianxiety Alprazolam	Reserpine, an alkaloid isolated from snake root (an Indian herbal medicine able to "calm violent lunatics") helped define the pharmacology of tranquilizers (c1944). The first antianxiety drug was described in 1946. This was unexpectedly found when testing a synthetic chemical developed as an alternative to tubocurarine (a neuromuscular blocking alkaloid isolated from vines).	A benzodiazepine lead was discovered by randomly screening chemicals for muscle relaxant and antianxiety effects in behaviorally suppressed rats (1958). Medicinal chemistry resulted in Alprazolam, a benzodiazepine with improved metabolism and reduced toxicity.

Plant Derived Bioactive Chemicals

USE/ NAME	ROLE OF NATURAL PRODUCTS	ROUTE OF DISCOVERY
Antibiotics Cefaclor , Ceftriaxone & Cefoxitin	A semisynthetic quinine derivative, ethylhydrocupreine was the first antibacterial chemotherapeutic agent introduced into medicine (c1911). Although antibiotic properties of microbial extracts were recognized since the the 19th century, penicillin was the first product used in a pure form (1941). Microbial fermentations are currently used to produce precursors of these antibiotics.	These antibiotic products were derived from the beta-lactam antibiotic, cephalosporin. Cephalosporins were discovered as part of a microbial screening program. The organism was isolated from a sample obtained from a sewer outlet (1948). Medicinal chemistry resulted in an increased spectrum of antibacterial activity and to the production of an orally active drug.
Anti-histamine Terphenadine (H1) Ranitidine & Cimetidine (H2)	Bacterial decomposition of ergot (a medicinal fungus which grows on wheat) gave a product which stimulated uterine contractions. Histamine was identified as the active principle (1910). Later it was proved to be present in animal tissue (c1926). This stimulated the search for an antagonist to overcome the toxic effect of histamine (1885).	Terphenadine resulted from extensive medicinal chemistry of piperoxan, a lead found by a random screen of chemicals which protect animals from histamine toxicity (c1937). The H1 class treat allergies and motion sickness. Leads for the H2 antihistamines were discovered by screening histamine analogs for gastric acid inhibition in rats (c1968). Medicinal chemists improved specificity and oral activity. They are used to treat gastric ulcers .
Anti-hypertensives Captopril & Enalapril	The ability of a snake venom to drastically reduce blood pressure was shown to be caused by its inhibition of angiotensin converting enzyme (1968). This enzyme produces an octapeptide which raises blood pressure and also destroys bradykinin which decreases blood pressure. Thus it became evident that a inhibitor of this enzyme could be an effective antihypertensive.	Angiotensin converting enzyme resembles carboxypeptidase A which was known to be inhibited by 2-benzylsuccinic acid. Based on this lead and on models of the enzyme active site, potential inhibitors were synthesized and tested for enzyme inhibition (1977). Medicinal chemistry improved the oral activity of these inhibitory peptide analogs.
Antipyretic Paracetamol	Quinine, isolated form cinchona bark and salicyclic acid, originally isolated from *Spirea ulmaria*, were the first drugs used as antipyretics. Acetylsalicyclic acid (aspirin) was synthesized to reduce unpleasant taste (c1898). Attempts to improve quinine resulted in the production of the synthetic quinoline antipyretics (1885).	The lead compound was acetanilide whose antipyretic effects were discovered by chance when this material was incorrectly administered in place of naphthalene, which was being tested for the treatment of intestinal worms (1886). Paracetamol, an analog with reduced toxicity, was prepared in 1893 but due to misleading toxicity data, was not marketed until 1953.

Plant Derived Bioactive Chemicals

USE/ NAME	ROLE OF NATURAL PRODUCTS	ROUTE OF DISCOVERY
Diuretic Hydrochloro-thiazine	Numerous herbs were known to induce mild diuresis. The xanthine alkaloids from tea, cocoa and coffee were identified as active chemicals. Theophylline, isolated from Camellia (tea) was three times as potent as caffeine and clinically used as a diuretic (1902) until replaced by more potent synthetic drugs.	Carbonic anhydrase was shown to be important in water resorption from the kidney because its inhibition by antibacterial sulphonamides caused alkaline diuresis (1942). A chemical which had undergone an unexpected ring closure to form a benzothiadiazine, was tested in a random screen for inhibitors of this enzyme (c1955). Medicinal chemistry increased the potency of this lead.
Female sex hormones Estrogenic Substances	The first attempts at hormone therapy used extracts of animal tissue (c1912). Some estrogenic compounds are found in plants but these a not medicinally important. However, plants are important commercial sources of synthetic precursors of these hormones.	Female sex hormones were isolated from ovarian extracts of animals (1929) using an assay based on changes in cells lining the vaginal walls of immature mice which paralleled those seen in the menstrual cycle of mature mice. Female sex hormones with reduced toxicity and improved activity have been developed by screening analogs of natural hormones.
Hypercholesterol-emia Lovastatin	Hydroxymethyl-CoA-reductase is an enzyme involved in the biosynthesis of cholesterol (c1958). It was rationalized that inhibition of this enzyme would reduce the levels of cholesterol which were involved in the development of atherosclerosis. Lovastatin, discovered in 1979 is a napthalenyl ester inhibitor produced by fungal fermentation.	This fungal metabolite was discovered by a mechanism based natural product screen. Extracts of diverse microbes are tested for inhibition of hydroxymethyl-CoA-reductase, an enzyme involved in the biosynthesis of cholesterol (1978). This product demonstrates the role of natural products in modern drug discovery programs.

**STATEMENT OF JOHN S. CROSSMAN,
EASTERN MUNICIPAL WATER DISTRICT,
BEFORE THE ENVIRONMENT AND NATURAL RESOURCES SUBCOMMITTEE,
UNITED STATES HOUSE OF REPRESENTATIVE
NOVEMBER 9, 1993**

Mr. Chairman, my name is John S. Crossman, and I am a Resource Development Administrator for Eastern Municipal Water District (EMWD). It is a pleasure for me to testify before the Environment and Natural Resources Subcommittee on EMWD's interest in and experience with plant species protected under the Federal Endangered Species Act. However, before discussing our experience with endangered plant species I would like to briefly describe EMWD and the area we serve.

EMWD is a progressive water district formed on October 16, 1950, pursuant to the Municipal Water District Act of 1911, as amended, State of California. A year after its formation, EMWD became a member agency of the Metropolitan Water District of Southern California to access imported Colorado River water. The original charter was authorized to provide an adequate water supply primarily for rural agricultural lands. As urban populations increased, the District added two other important areas of service: sewage collection, transmission, and treatment; and water reclamation.

EMWD's service area is located in western Riverside County in southern California (Figure 1). It is approximately 539 square miles with a population of 395,000. The EMWD headquarters are located approximately 70 miles east of Los Angeles and about 30 miles southeast of Riverside in the cities of Hemet and San Jacinto. The service area includes portions of the San Jacinto and Santa Margarita watersheds and has the physical characteristics typical of the interior basins of southern California. The District is bounded on the east by the San Bernardino National

Forest and the San Jacinto Mountains, on the north by San Bernardino County, on the south by San Diego County, and on the west by the Cleveland National Forest and the western edges of the Perris and Menifee Valleys. Elevations range from 1,000 feet in the southern portions of the service area to 3,140 feet near Polly Butte. Immediately east of the district is Mt. San Jacinto, which rises to 10,805 feet above sea level.

The climate of the area is dry, semiarid, near-Mediterranean zone typical of the moderately elevated basins of southern California. The climate is characterized by wet and dry seasons with an average annual temperature of 62 F, generally low precipitation with an average annual precipitation of 12.7 inches, and mild winter temperatures resulting in an average frost-free period of 247 days.

Demographically, western Riverside County is one of the most rapidly changing in the State of California. Rural agrarian lands are giving way to suburban growth with accompanying shopping centers, schools, and transportation corridors. The population is increasing and the amount of agricultural land and open space is decreasing. Local planning agencies project that agricultural land use in the EMWD area will decline from 95,320 acres in 1990 to 46,550 in 2005, a 49 percent decrease over the next 15 years.

The EMWD area contains five incorporated cities: Moreno Valley, Temecula, Perris, San Jacinto, and Hemet. Their populations range from 13,700 to 101,300. The majority of land use is presently low density residential, which includes single family dwelling units at densities of up to

four units per acre. Higher density residential areas and commercial and industrial zones are centered around the incorporated and unincorporated communities. Mobile home parks represent a high percentage of existing dwellings units in the Hemet/San Jacinto area and in Sun City. A high concentration of dairy farms is found northwest of San Jacinto along the San Jacinto River. Large open spaces are still present throughout the area.

In 1992/93 EMWD served approximately 65,00 acre-feet (AF) of water (one acre-foot of water is 325,990 gallons of water) to 72,000 domestic/commercial/industrial customers. Approximately 80 percent of the District's water is supplied by MWD through its Colorado River Aqueduct and the California Aqueduct with the remaining 20 percent produced locally. Agriculture accounts for 20 percent of the water used, with the remainder going to the other uses. To ensure adequate supplies and meet fire-flow requirements, the District has 115 million gallons (MG) of storage with an additional 58 MG under design or construction. Within the next 5 years this is projected to increase by an additional 68 MG.

The District has five regional water reclamation facilities with a total capacity of 43 million gallons per day. In 1992/93 they produced an average of 25 million gallons of reclaimed water per day. Four of the regional plants provide tertiary treatment which effectively removes bacteria, viruses and virtually all suspended solids. At this level of treatment, reclaimed water can be used for almost any use short of direct human consumption. The remaining treatment facility provides secondary treatment which employs biological oxidation to remove 85-95 percent of the suspended solids and other impurities. This water can be used on fiber, feed and seed crops

not eaten directly by humans.

Population projections for the District's service area, indicate continued growth for the foreseeable future although not at the rates experienced in the late 1980's. Two recently developed growth scenarios are indicated below.

Projection	1990	1995	2000	2005
Option 1 (Low)	305,300	377,600	449,800	533,500
Option 2 (Moderate)	340,300	455,400	609,430	815,550

To meet the projected water and sewer demands for this projected growth, EMWD is in the third year of a 20-year capital improvement program, i.e, 1990 to the year 2010. Over the next 5 years, this will involve more than 250 projects and system improvements at a estimated cost of $500 million. Because of the uncertainty of imported water both in the terms of cost and availability, EMWD's Board of Directors has made the development, management, and protection of local water supplies the District's highest priority. Stated another way, EMWD has made water conservation, reclamation of treated wastewater, and groundwater resources management its highest priority. These efforts have resulted in local water projects that are considered at the "cutting edge" of responsible resources management. Representative projects include:

1) Water Conservation - Programs targeting indoor and outdoor uses are expected to save 1,900 AF per year by 1995. Landscape conservation measures through local ordinances, are projected to save an additional 4,700 AF per year by 1995.

2) Groundwater Recharge - Through direct injection and controlled percolation, reclaimed water will be used to recharge local groundwater basins. Planned recharge projects are expected to increase groundwater yields by approximately 15,000 acre-feet per year (AF/yr) by 2005.

3) Hemet/San Jacinto Groundwater Augmentation - Underground storage of surplus imported water and "harvested" stormwater. This will provide approximately 30,000 AF/yr by 2010. (Note - Harvested stormwater is water captured during rainfall events that is used to recharge groundwater basins. This is typically done by creating side stream impoundments in areas with high percolation rates.)

4) Multipurpose Wetlands Projects - Water resource management projects that utilize wetlands to (a) treat, store, and recharge secondary treated wastewater; (b) treat nitrate contaminated groundwater; and (c) to temporarily store brines from a desalinization unit before final disposition.

5) Multipurpose Corridor Project - Creation of multipurpose utility corridors along the San Jacinto River and Salt Creek drainages that link open space, rural and urban lands, and parks

and recreation facilities (Figure 2). These corridors will be designed to serve as wildlife movement corridors and will include features to capture stormwater runoff for groundwater recharge.

6) Brackish Groundwater Desalination - This year the District initiated design and construction activities for a desalinization plant to treat contaminated water from the Menifee Groundwater Basin. This technology will not only treat saline groundwater basins but will allow EMWD to address the salt balance issue associated with the use of reclaimed water. Over the next 10 years, the District plans to construct up to 3 desalination facilities to treat saline groundwater which presently threatens to contaminate adjacent, usable groundwater supplies. These plants will produce up to 12,000 AF/yr by 2005.

IMPACT OF ENDANGERED SPECIES

By late 1992, the Federal Endangered Species Act (ESA) protected 1,277 plant and animal species with 113 of those found in California. These protections have resulted in the designation of approximately 144,000 acres, or more than 40 percent of EMWD's service area as sensitive habitat. (Note: The 144,000 acres includes 54,000 acres of coastal sage scrub habitat type, which is critical to protecting the California Gnatcatcher.) With the recent addition of the California Orcutt Grass and the expected listing of the San Jacinto Saltbush, this total is expected to increase even more.

Southwest Hemet Sewer Pipe Line - Within the last year, EMWD has experienced two incidents with endangered plant species. The first incident involved a 7.4 mile sewer line in the southwest Hemet/Winchester area. The proposed alignment passed through a heavily disturbed area (from agricultural practices) that had been zoned for commercial/industrial use in the City of Hemet's General Plan (1992). Prior to the adoption of the General Plan, EMWD had published an environmental assessment in October 1991 requesting comments on the proposed pipeline alignment. When no comments were received from either the public or the natural resource agencies, EMWD proceeded with project construction in October 1992. However, before construction started new information became available on potential sensitive species in the zoned area. A focused biological survey was immediately undertaken and completed by the end of November. The field survey indicated the presence of sensitive plant species in an area of alkali sinks and vernal pools not previously detected. The impacted area involved a 2.6 acre parcel and a 0.5 acre parcel. Following these disclosures, EMWD met with the U.S. Fish and Wildlife Service (Service). The Service recommended offsite mitigation at a 1:11 ratio, development of a restoration plan, and mitigation monitoring. The estimated cost for additional offsite land acquisition was $385,000. After 5 months of unsuccessful negotiations, the EMWD Board of Directors approved an alternative alignment along a local highway at an added cost of $530,000.

The major plant species of concern was California Orcutt Grass which has recently been added to the Federal endangered species list (**Federal Register**, August 3, 1993). The grass is approximately 7 to 8 inches tall and is found in alkali soils such as a vernal pool habitat complex.

The grass is detectable primarily during the spring (May to June) and, in Riverside County, the only other known locations are Skunk Hollow and the Santa Rosa Plateau. With the addition of the southwest Hemet siting, there a now three known locations in western Riverside County. The other species of concern is the San Jacinto saltbush. The distribution of this plant is restricted to western Riverside County, primarily to the San Jacinto River and Salt Creek floodplains and to alkali lands between these waterways. This annual plant blooms from May throughout August. Following the blooming period it dries and becomes extremely difficult to detect.

Reach V Reclaimed Water Pipeline - The Reach V pipeline is a 24 inch reclaimed water pipeline that was constructed along the San Jacinto River in the east Hemet area in late 1991 and 1992. During the course of project construction, a University of California - Riverside professor, noted the ongoing construction. While inspecting the site, he noted that the December rains had caused local plants to germinate, one of which was the endangered Slender Horned Spineflower (**Federal Register**, October, 1987). This sighting resulted in the stoppage of the project. Negotiations with the Service and the California Department of Fish and Game resulted in a new alignment. The total cost of the realignment was $88,000.

The Slender Horned Spineflower is a prostrate annual with leaves in a basal rosette. The plant sends up a flowerstalk, 6 - 7 inches high. The plant is found in sandy-silt, alluvial soils that are deposited in fans where streams emerge from ravines onto a flood plain. The species is endemic to the flood plain benches and terraces of Los Angeles, San Bernardino, and Riverside

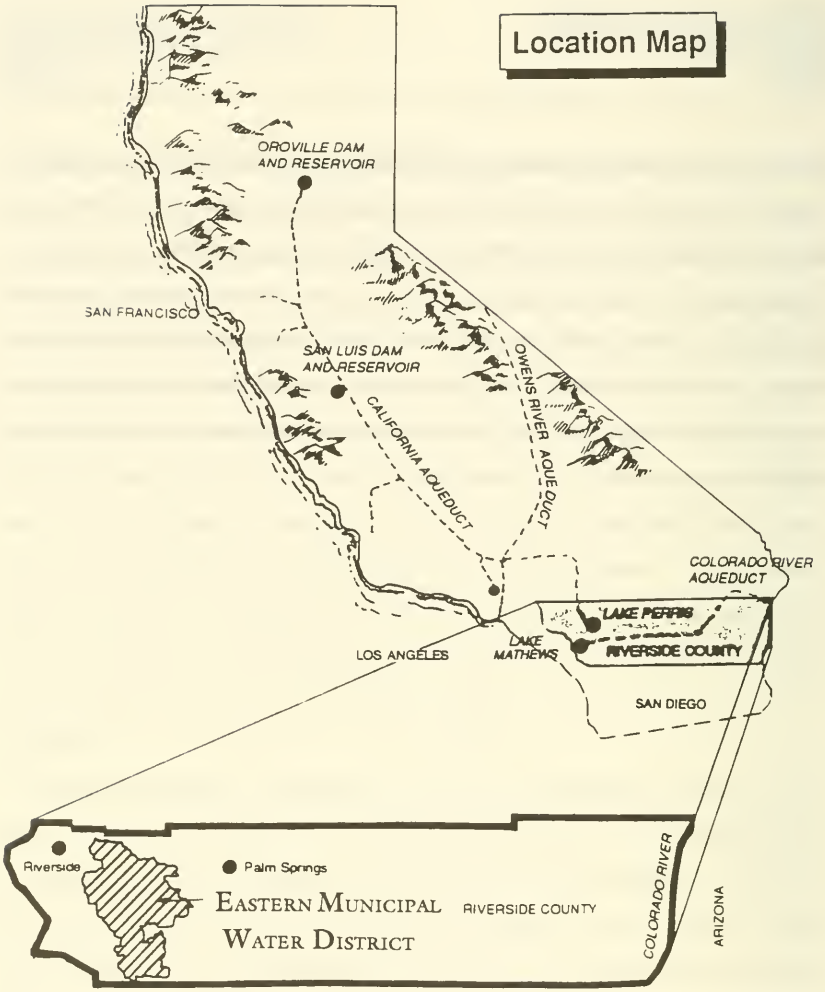
counties. The known area of remaining habitat totals less than ten acres.

To accommodate endangered species concerns, EMWD has added additional staff to address these issues in the project formulation and design phase, acquired a GIS data base for threatened and endangered species, provided biological survey information to the U.S. Fish and Wildlife Service and California Department of Fish and Game to update their data base, and retained environmental specialists to work with staff on ESA issues. In addition to these steps, the District has adopted and implemented an endangered species policy. The policy specifically seeks to avoid any impacts to sensitive species and their habitat. If avoidance is not possible, EMWD will minimize the impact and mitigate for any unavoidable impact. To implement this policy the District now requires a site visit and biological survey for each project area prior to actual project design. It is estimated that these steps and future mitigation costs will add approximately 25 percent to the cost of all future projects.

SUMMARY

The Endangered Species Act represents this Nation's commitment to protecting natural resources and preserving biodiversity. However, the current species by species habitat approach is undermining the original intent of Congress. More and more the regulatory agencies find themselves administering the Act as a land use, growth limitation statute instead of a species protection statute. This regulatory dilemma has led to conflicts with state, county, and local authorities responsible for making land use and economic growth and development decisions.

Eastern Municipal Water District supports environmental protection and conservation programs. However, as a public agency that works directly with local and state government as well as state and federal regulatory agencies, EMWD is becoming increasingly frustrated in its efforts to provide basic water and sewer services. Increasingly stringent and confusing regulatory requirements are not only causing projects delays, but costs that do not provide real species benefits. If fundamental problems with the Act are not resolved, the associated regulatory burdens threaten to outstrip available financial resources and will impact public agencies ability to serve their customers.


Location Map
OROVILLE DAM
AND RESERVOIR
SAN FRANCISCO
SAN LUIS DAM
AND RESERVOIR
CALIFORNIA AQUEDUCT
OWENS RIVER AQUEDUCT
COLORADO RIVER
AQUEDUCT
LAKE PERRIS
RIVERSIDE COUNTY
LOS ANGELES
LAKE
MATHEWS
SAN DIEGO
Riverside
Palm Springs
EASTERN MUNICIPAL
WATER DISTRICT
RIVERSIDE COUNTY
COLORADO RIVER
ARIZONA

Preliminary Plan of Habitat Corridors

The area is home to several threatened, rare, and endangered species including:

- Least Bell's Vireo
- California Black Rail
- Bald Eagle
- California Yellow-Billed Cuckoo
- Stephens' Kangaroo Rat
- Desert Bighorn Sheep

The richly biological diverse area is located between the habitat aree of the San Bernardino National Forest, San Jacinto Wildlife Area and the Cleveland National Forest. Natural migratory routes between habitat areas cross tha MPC.

The Berry Botanic Garden
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November 9, 1993

Congressman Gerry E. Studds, Chairman
Subcommittee on Environment and Natural Resources
U.S. House of Representatives
Committee on Merchant Marine and Fisheries
Room 1334, Longworth House Office Building
Washington, DC 20515-0260

Congressman Studds, Members of the Committee, Ladies and Gentlemen:

I am Linda McMahan, Executive Director of The Berry Botanic Garden in Portland Oregon. I hold graduate degrees in botany and law, and have studied how endangered plants laws have been passed and implemented, primarily in the states. Conservation of our nation's plants and other natural resources is an important issue to me. In this regard, I chair the Conservation Committee of the American Association of Botanical Gardens and Arboreta. I am also honored to serve as a Member of Oregon's Environmental Quality Commission, which oversees the activities of the Department of Environmental Quality.

1. The first point I would like to make today is that botanical gardens are already working to conserve plants both here and abroad. We in botanic gardens are not waving the flag about issues so much as rolling up their sleeves and getting to work. The larger botanical gardens, such as those in New York and St. Louis, Missouri, have major programs to work on both native and tropical plants in many realms of science and conservation, including assessing the economic value of plants worldwide. Smaller botanical gardens have their own programs.

I am very proud of my own institution. We are small, with a total annual budget of about $300,000. Yet in 1983, we became the first botanical garden in the country to set up a regional seed bank for rare and endangered plants. Over 1 million seeds from over 250 different kinds of plants are now stored in sub-zero storage. The Garden is currently working on nine different projects to conserve plants cooperatively with state and federal agencies such as the Bureau of Land Management, the U.S. Forest Service, and the U.S. Fish & Wildlife Service. With relative modest investment and a clear view to our potential, mission, and horticultural skills, even a small institution like The Berry Botanic Garden has been able to accomplish much when these are paired with the land management agencies. Much more, however, remains to be done.

The Logo, *Primula cusickiana*, a small alpine of Oregon's Wallowa Mountains, produces tiny, but abundant purple flowers. Its rarity, beauty, and exact horticultural requirements symbolize the Garden's effort in conservation, preservation, and [illegible]

2. Secondly, I wish to applaud the efforts of the individual 50 states to conserve their own rare and endangered plants. Over half of the states, 26, have passed some kind of endangered plant law. These laws vary greatly in their provisions. The typical state law provides for a listing process and prohibits commercial sale without permits or prohibits taking from another person's land without permission.

A few state programs stand out as particularly strong because of their implementation or legal provisions. These include Massachusetts, the most recent state to pass such a law, which extends protection to endangered and threatened plants on private land. California has a strong provision for coordinating the activities of other state agencies when their activities affect rare plants. Ohio, even with a rather weak law, has made tremendous progress through an aggressive public information campaign. And North Carolina has the best nursery regulations in the nation for controlling commercial activity of rare or endangered plants.

These state efforts can be and are being greatly assisted by federal activities including the Endangered Species Act. Money allotted to the states through Section 6 funding is essential to keeping many of the state programs intact and working effectively. The increase in botanists in recent years in the federal land management agencies is a particular boon to the western states, where large amounts of land in federal ownership and a high number of rare and endangered plants meet. Increased funding to these agencies for plant survey and protection activities has allowed for increased information and better conservation strategies. These surveys have revealed that some species are more commonly than once thought, allowing officials to remove these species from listing consideration. A small portion of that funding is provided to organizations like The Berry Botanic Garden who are working with the agencies, often sharing equally the cost of the projects themselves.

3. Thirdly, I would like to address briefly the medicinal use of these plants. In short, I estimate that more than half of the rare and endangered plants in this country are related to plants of known medicinal use. Specifically for this hearing, I analyzed a list of plants considered rare or endangered in Oregon, Washington, and Idaho, a total of 556 different species, in 112 different genera. I cross-referenced this list to plants of known economic value. The results of this impromptu survey were not surprising to me, although they are dramatic. Of the 556 total species, 349 or 63 percent are related to plants of economic value for food, medicine, utilitarian purposes, or as poisons.

The highest value was for medicinal use. A total of 277 of the species--just under 50 percent--are related to plants of known medicinal use or which were used medicinally by Native Americans.

When you think about this carefully, it is not surprising. Plants have been evolving and adapting to their habitats for thousands of years. In so doing, they have

not only adapted to special conditions of their soil, but have developed defenses against being eaten by grazing animals, insects, against fungal and bacterial diseases, and to help deter other nearby vegetation and thus gain a competitive advantage in their habitats. How have they done this? The answer is through chemistry--chemicals they make themselves. Every one of theses chemicals is a biological agent, because it affects other organisms. Think of a plant as a tiny biological weapons factory. Our common names for these plants like "fleabane," "wormwood," "locoweed", and "bugbane," are clues to their usefulness.

We, the human species, are beneficiaries of this plant activity. What may work as a deterrent of some sort in *Podophyllum peltatum*, the may apple, was used by Native Americans to treat warts and as a laxative. In modern uses, it yields the chemical podophyllotoxin, part of our biological arsenal to treat cancer. A poison in foxglove (*Digitalis purpurea*), introduced by Europeans to this country, yields a powerful heart medicine. Wood of the Pacific Yew (*Taxus brevifolia*) always considered resistent to decay by Native Americans of the Pacific Northwest yielded taxol, a modern an important treatment for cancer. Alkaloids which deter grazing or insect infestation find multiple uses as stimulants, immune system treatments, cancer treatment, and many other uses.

A number of plants have gained increased attention of late because of their possible uses in treating diseases of the immune system. These include *Astragalus membranaceous*, a plant from China, and three American species, *Echinacea purpurea*, *Ligusticum porteri*, and *Lomatium dissectum*, all of which were used medicinally by Native Americans. Notably, all of these genera have closer relatives, within the same genus, already listed as Endangered or Threatened, or which are candidates for listing.

Economic uses do not end with medicinal potential. Plant chemicals find uses is industry, as natural pesticides, for example. Other plants, adapted to specific soils or conditions, can become gold or other mineral indicators to the geobotanist. They may even concentrate certain chemicals in their tissues. Plant oils have found use in industry as high quality lubricants. Relatives of economic plants, such as those rare and endangered in this country are an important resource.

4. Considering that up to an estimated 20% of the kinds of plants native to the United States are rare or endangered, we stand to loose a major part of this resource unless conservation activities through the Endangered Species Act or other means can slow the loss. I believe that by far the most effective and least expensive methods are through conserving the species on the land they already occupy. This is the premise of work at The Berry Botanic Garden and every other major conservation organization working with endangered plants today.

Any effort to use or strengthen the Endangered Species Act or other legislation to help in the conservation effort will be important. This action could take many forms, including additional prohibitions in the Act, increased funding for plant conservation activities, tax-relief for conservation activities by private or corporate landowners, or increased funding to state governments with strong plant conservation programs. I believe that such credible conservation actions are compatible with continued economic growth of our nation.

Thank you for the opportunity to participate in the hearing today on this most important issue.

Yours sincerely,

Linda R. McMahan, Ph.D., J.D.
Executive Director

Pfizer Inc
235 East 42nd Street
New York, NY 10017-5755
Tel 212 573 3558 Fax 212 573 1853

December 9, 1993

C. L. Clemente
Senior Vice President—Corporate Affairs

The Honorable Gerry E. Studds
U.S. House of Representatives
Subcommittee on Environment and
Natural Resources
Room 546 Ford House Office Building
Washington, D.C. 20515

Dear Mr. Chairman:

In response to your request, we are submitting a written statement for the record in regard to the Subcommittee's hearing held on November 9, 1993, on the medicinal uses of plants and the protection afforded to plants under the Endangered Species Act. We appreciated your invitation to submit written testimony on our recent collaboration with the New York Botanical Garden. We believe it is a collaboration that will benefit both Pfizer and the Garden, and hopefully the public, with the discovery of new sources of medicines to treat diseases.

As requested, enclosed are five copies of our written statement. Again, thank you for inviting Pfizer to submit written testimony.

Sincerely,

Constantine L. Clemente
Senior Vice President
Corporate Affairs

Written Testimony of

Pfizer Inc

Submitted to the

Subcommittee on Environment and Natural Resources
House Committee on Merchant Marine and Fisheries

for the Hearing on Medicinal Uses of Plants
and the Endangered Species Act held November 9, 1993

Pfizer Inc Programs for the Discovery and Development of Novel Therapeutic Agents from Natural Sources

December 9, 1993

Introduction

Pfizer is a research-based, diversified health-care company with its major research facilities in Groton, Connecticut. Pfizer employs 44,000 people worldwide and had sales of $7.23 billion in 1992. In September 1993, Pfizer announced a three-year, $2 million research collaboration with The New York Botanical Garden to study plant extracts as a possible source of new medicines. This collaboration, and its role in the overall Pfizer drug discovery effort, is the focus of our written testimony. In addition, we present our views on the adequacy of the Endangered Species Act to provide further conservation of plant species.

Drug Discovery

Biomedical researchers today have access to technologies unthought of five years ago. The research tools of molecular biology have provided us with an understanding of the underlying mechanisms of many diseases at the molecular level, and this knowledge of disease mechanisms is growing at an ever-increasing rate. It seems that each week there is an announcement of a major breakthrough in our understanding of some disease. Recent examples of such breakthroughs include important insights into the molecular basis of Alzheimer's disease, Cystic Fibrosis, and AIDS. This knowledge and the dazzling array of research tools that molecular biology also has provided are revolutionizing the discovery process of new therapeutic agents. However, as our understanding of diseases increases and our development of molecular tools for research programs continues, the entire process remains limited by our ability to find molecules to intervene at the desired targeted disease mechanism.

Our search for novel therapeutic agents takes several forms: our organic chemists synthesize compounds; we examine fermentation extracts from a wide range of microorganisms and have looked closely at spider venoms. Recently, we have begun to look at extracts and compounds isolated from plants. This activity includes our newly announced collaboration with The New York Botanical Garden.

Pfizer/The New York Botanical Garden Research Collaboration

The Pfizer/The New York Botanical Garden research collaboration provides us with an exciting opportunity to examine the flora of the United States for potential new therapeutic agents. Plants have been a source of disease treatments for thousands of years. However, isolating the key substances for development as a pharmaceutical has, until recently, been impractical. The emerging new research tools and knowledge of molecular biology make it possible to review large numbers of substances using small amounts of plant material. Where in the past, pounds of plant material would have been required, now only a fraction of an ounce is necessary to conduct extensive experimentation. Furthermore, modern analytical techniques allow us to determine the molecular nature of the active component in an extract with minute quantities of material. The requirement of such small quantities of material means that the collecting activity will not have an adverse impact on the environment.

In our collaboration with The New York Botanical Garden, botanists from the Garden will travel throughout the United States to collect plant samples. From our perspective, it was vital that the collecting be done by trained professionals for two reasons. First, it is desirable that this plant survey be as broad as possible. Second, it is extremely important

that the collecting activity be sensitive to rare and endangered species. The collected plant material will be returned to the Garden where samples are extracted; the extracts are then provided to Pfizer.

As with all good collaborations, both parties benefit. Pfizer gets access to the botanical expertise of the Garden botanists and the opportunity to explore the medicinal potential of extracts from a diverse array of plants. While on collecting trips, the Garden personnel are contributing to a survey of the flora of the United States, documenting the locations of the plant species they encounter. In addition, the Garden is able to use the plant material and extracts for educational purposes.

Endangered Species Act (ESA)

The Subcommittee has requested Pfizer's views on the adequacy of the ESA to provide for the long-term conservation of listed plant species. We would like to preface those comments with a recent experience we had in research in higher plant natural products. An extract from a temperate zone plant showed biological activity in one of our assays. As a next logical step, extracts from closely related species were then tested. To our surprise, the extracts from the related species were completely inactive. Analysis of the extracts from both the active, initial species tested and the inactive, related species revealed that the activity could be attributed to what is probably a single biological step unique to the initial plant species. The inference that can be drawn from this observation is that a single gene difference was responsible for the activity we detected in our assay. Although it is far too early to say whether this active compound will ever become a pharmaceutical candidate, it is sobering to contemplate such subtle differences resulted in an active compound. The ESA, intended for the protection of

endangered plant species, by our reading appears to be adequate and we urge its reauthorization.

Conclusion

As a health-care company, we find ourselves with many research opportunities before us. Modern biological research tools are providing us with unprecedented opportunities to make great strides in the development of novel therapeutic agents for the treatment of human diseases. We believe that plants will play an important role in the development of such novel agents. Our own experience shows that it is impossible to determine before the fact which individual species may or may not be useful for some current or future propose. Consequently, it will be important to ensure that endangered species are protected, yet at the same time, are available for medicinal study. Pfizer's collaboration with The New York Botanical Garden seeks to accomplish both of these objectives.

AMERICAN FARM BUREAU FEDERATION

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December 8, 1993

The Honorable Gerry E. Studds, Chairman
House Merchant Marine and Fisheries Subcommittee
on Environment and Natural Resources
U.S. House of Representatives
545 Ford House Office Building
300 D Street, SW
Washington, DC 20515

Dear Chairman Studds:

Please find enclosed, our statement to the subcommittee regarding the hearing on November 9, 1993, addressing protections provided to plants under the Endangered Species Act. We appreciate the opportunity to enter our comments into the hearing record as well as your consideration of our views on this issue.

Sincerely,

Richard W. Newpher
Executive Director
Washington Office

Enclosure

STATEMENT OF AMERICAN FARM BUREAU FEDERATION TO THE SUBCOMMITTEE ON ENVIRONMENT AND NATURAL RESOURCES OF THE HOUSE COMMITTEE ON MERCHANT MARINE AND FISHERIES

REGARDING PROTECTIONS PROVIDED TO PLANTS UNDER THE ENDANGERED SPECIES ACT

November 9, 1993

The American Farm Bureau Federation, the nation's largest general farm organization representing the interests of more than four million member families, appreciates the opportunity to present this statement on the protection of plants under the Endangered Species Act.

At an October 13, 1993, hearing, Chairman Studds spelled out the challenge to be addressed at the hearing in the following terms:

> "I think it is quite clear that unless we can satisfy the legitimate and rational, and I underline legitimate and rational, concerns, and they are these, of those who are focused on the problem of private property rights, we are not going to be able to successfully sustain [the Endangered Species Act], period. So this—that—is abundantly clear, I think, and everyone ought to recognize that."

Also:

> "So to the extent that anyone can offer constructive ideas dealing with the problem, then they will have made a major contribution to our efforts to extend the Endangered Species Act itself."

It is in this spirit that we offer the following statement.

The witnesses at the November 9, 1993, hearing on this subject addressed the possible beneficial effects that might accrue from protecting endangered or threatened plants. But none of those witnesses offered suggestions for protecting such plants while at the same time protecting private property rights. We offer a suggestion for addressing both issues.

The perceived benefits of the Act extend to the public at large. All of the witnesses testifying on November 9 detail the discovery of new medicines that have benefitted the entire public. Yet, under the current Act, most of the cost of breeding, feeding and sheltering these species falls upon those few people on whose property they happen to be found. Costs of protecting such species that benefit the general public should be borne by the general public. That is the requirement of the Fifth Amendment to the Constitution.

There is no question that the brunt of the Endangered Species Act—as applied to both plants and animals—falls primarily on our nation's farmers and ranchers. The vast majority of the remaining privately owned "open space" is owned by agricultural producers. The success of the Act depends on the cooperation of farmers and ranchers.

It is clear that the current structure and application of the Endangered Species Act does not foster the necessary cooperation. To the contrary, the punitive nature of the Act as administered has created an adversarial relationship that affects both private property rights and is to the detriment of the listed species. Under current law, farmers and ranchers are prevented from making full and effective use of their property, and are prevented from protecting their property because of the burdens created by the Act. Should you desire, we would be more than happy to provide the committee with such examples.

Listed species have also suffered from current application of the Act. Despite the seemingly absolute prohibitions in the Act, far more listed species have still become extinct than have been recovered. It is becoming increasingly clear that habitat preservation—without management—is insufficient to protect species.

Clearly, a new approach is called for.

We believe that endangered species protection can be more effectively achieved by providing incentives to private landowners and public land users than by imposing land use restrictions and penalties.

To this end, we propose the adoption of a landowner incentive program that would enhance both the protection of listed species and private property rights. An outline of the proposal is attached to this statement.

Under the proposal, the Interior Secretary would enter into voluntary agreements with private landowners in those areas designated as critical habitat to conserve and manage the species on their property. To better balance the interests of man and species, critical habitat would be a defining factor in delineating the scope of the program, since critical habitat is defined as the area essential for the existence of the species.

The Secretary would provide technical assistance and administration through the Fish and Wildlife Service and annual payments, determined by bid process, to owners and operators for protection and management of species and habitat.

Most farmers and ranchers—given appropriate incentives—would willingly participate.

A key aspect of the proposal is that private landowners would manage both the species and prescribed habitat for the conservation of the species. Scientists are more and more realizing that preservation of habitat is not enough—species require active management if they are to recover. The attached news article detailing the story of the Peter's Mountain Mallow in Virginia illustrates this point. Left alone, without active management by such measures as controlled burns, this species may have gone extinct. Who better to provide that management than the person who knows the property and is there to provide necessary management measures?

We submit that this proposal is more cost-effective use of funds than either having the government provide the management, or having no management at all.

For that crucial reason, our proposal favors active management agreements to a program of conservation easement acquisition, which might preserve habitat but provides no guarantees of needed management.

Our proposal also protects the rights of property owners, because landowners will voluntarily work to protect listed species. Under our proposal, they will also be provided the direction and means for accomplishing that protection. The requirements of the Fifth Amendment will also be satisfied, because the protection of species that are to be conserved for the benefit of the general public will be paid by the general public. In effect, participants in the program will be paid to protect and help recover listed species.

A major concern of rural communities is the increasing loss of taxable base property when property is withdrawn from productive use. Rural economies in areas of large federal land ownership or where significant land use restrictions are in place, have already been stretched to the limit. Thus, any withdrawal of property or diminution in taxable value occasioned by the program will have to be offset with appropriate compensation to local communities.

The five-year agreement term in this proposal coincides with the five-year status reviews required under the Act, and would provide a measurable and accurate baseline and assessment of such status.

These are only some of the highlights of our proposal.

Our proposal is premised on the following factors:

- that more can be accomplished by providing incentives than by land use restrictions and prohibitions;
- that active species management is more beneficial to species recovery than mere habitat preservation;
- that private property rights can and must be respected; and
- that day-to-day monitoring and management by the person on the ground is better and more cost-effective than attempted government management.

This is a serious proposal offered in good faith. We submit that it is the best plan we have seen to date that would answer the challenge of the Chairman to protect both listed species and private property rights. It will promote a partnership and spirit of cooperation between the government and the private sector for the protection and recovery of listed species that is so sorely lacking today, and that keeps the Act from being successful. In the process, it will show that the interests of listed species and the interests of private property rights can co-exist.

We hope the committee will give serious consideration to enactment of an incentive-based program for protection of listed species and habitat along the lines that we have proposed. We look forward to working with the committee to develop this idea further.

Attachments

Endangered Species Private Land Conservation and Protection Program

I. PURPOSE

A. To develop a voluntary cooperative effort between the U.S. Fish and Wildlife Service (USFWS) and cooperating private land owners for the establishment of Critical Habitat Reserves (CHR) to protect threatened and endangered species.

B. Protect constitutional property ownership rights of private land owners.

II. CRITICAL HABITAT RESERVE

A. General Provisions

1. The Secretary of Interior (Secretary) will contract with cooperating land owners/operators to provide Critical Habitat (CH) and land owner/operator management of the CH for the protection of threatened and endangered species.

2. No more than 25 percent of the land mass or water bodies in any one county will be placed in a CHR unless additional areas would not have an adverse effect on the local economy.

3. Contracts will be for 5 years and renewable only if the presence of a threatened or endangered species exists.

B. Duties of the Secretary

1. In return for a contract, the Secretary shall:

a. Provide for the cost of carrying out the CHR program.

b. Pay annual rental and management fee during the term of the contract to the land owner/operator for the conversion of private property uses to the CHR.

c. Provide technical assistance and management training to cooperating land owners/operators through the USFWS.

d. Consult with the Secretary of Agriculture to ensure that the program is harmonious with programs of the U.S. Department of Agriculture (USDA).

C. Payments

1. The Secretary shall provide payment for obligations incurred:

a. With respect to the cost of CH preservation.

b. With respect to management fees.

c. With respect to annual rental:

i. Upon signing of a contract with a land owner/operator and on each anniversary date of the contract.

d. The amount of rent shall be determined by a rental bid from the land owner/operator.

e. Payments shall be made in cash.

f. Endangered species CHR program shall not be subject to payment limitations.

g. Payments shall be independent of any other payments on the same land or water body.

2. The Secretary shall provide payment for lost revenue to local government entities as a result of CH designation:

a. With respect to revenue paid "in lieu of taxes" to local governmental entities from the sale of timber from national forest lands.

b. With respect to revenue paid to local governmental entities derived from the lease or rental of grazing rights on Bureau of Land Management lands.

D. Contracts

1. A contract shall continue in force for the 5-year duration.

a. If land ownership/operator changes occur during any contract period, the new land owner/operator may enter into a new 5-year contract period on the anniversary date of the contract in force at the time of the acquisition if the presence of a threatened or endangered species exists.

2. Contracts shall not prohibit any agricultural use of land or of a water body placed in the CHR program unless that use is proven by sound scientific bases to jeopardize the existence of threatened or endangered species.

3. The Secretary may modify a contract only if the owner/operator agrees.

4. The Secretary may terminate a contract only if the owner/operator agrees.

5. Public access shall be allowed only if the land owner/operator agrees and the agreement is openly stated in the contract.

6. Contracts shall be in lieu of statutory recovery plans for the same species on the same land or water body.

E. Duties of Land Owners/Operators

1. The land owner/operator must agree:

a. To implement an approved CHR plan.

b. Not to use CHR land for purposes other than those provided for in the contract.

c. To periodic inspections to determine compliance with the contract.

d. On violation of a term or condition of the contract:

i. Forfeit all rights to rental and management fees and refund payments with interest to the Secretary; or

ii. To refund or accept adjustments to rental and management fees; and

iii. The Secretary will determine if the violation should or should not warrant termination of the contract.

F. Special Provision

1. Crucial Critical Habitat (CCH) — a site-specific habitat without which a threatened or endangered species could not survive.

a. If a land owner/operator and the USFWS are unable to agree on program participation in areas that are determined to be CCH, an arbitration panel knowledgeable of the value of the CCH in relation to the survival of the species, shall resolve the differences between the land owner/operator and the USFWS.

III. OVERALL ADMINISTRATION OF THE PROGRAM

A. Responsibilities of Congress

1. Appropriate funds to adequately carry out the program.

B. Responsibilities of Federal Agencies

1. U.S. Fish and Wildlife Service

   a. Develop accurate scientific data for the determination of threatened and endangered species and CH.

   b. Development CH boundaries based on current actual range of the affected species.

   c. Provide technical assistance and management training to cooperating land owner/operators.

   d. Conduct public hearings concerning proposed CHR designations and provide public notice through the Federal Register and local newspapers.

   e. Notify each affected land owner/operator of the proposed CHR designations by registered mail.

   f. Make inspections and evaluations of the progress of each privately-managed CH.

2. U.S. Department of Agriculture

   a. Assist USFWS with boundary delineation of agricultural land.

   b. Provide CHR planning to maintain soil and water integrity.

   c. Review proposed CHR to prevent conflicts with current USDA programs.

   d. Review contracts to ensure acceptable agricultural land and water management practices are followed.

3. U.S. Department of Labor

   a. Provide a retraining program for persons displaced from jobs as a result of CHR program designations.

C. Responsibilities of State Agencies

1. State Fish and Game Agency

a. Assist the USFWS with technical assistance and training for cooperating land owners/operators.

2. Land Grant Universities

a. Develop training and educational materials for the CHR managers.

3. State Soil and Water Agencies

a. Assist USDA with CHR planning to ensure soil and water quality.

D. Responsibilities of Local Governments

1. County Property Appraisal Agency

a. Develop an equitable method of appraisal for land entered into the CHR program.

IV. ADMINISTRATION

A. Final CHR determinations shall be made jointly by the Departments of Interior and Agriculture.

B. The Secretary of Interior shall develop an appeal procedure for persons adversely affected.

1. Persons affected would be those who could:

a. Show infringement on their private property rights.

b. Show substantial economic harm as a result of a CHR designation.

C. The violation of a contract by one operator shall not affect the contracts of other operators of land of a common land owner.

D. The interests of, in any single contract, shall be protected with respect to the sharing, on a fair and equitable basis, of the rental payments contracted for in the CHR program.

THE WASHINGTON POST

by Boyce Rensberger

One of the world's most endangered plants, the Peter's Mountain mallow, was down to just four known individuals in 1991 before it was rescued by setting fire to its habitat in southwestern Virginia's Giles County. Now, according to a report by the Nature Conservancy, which owns the land, there are hundreds.

The mallow, Iliamna corel, is a perennial that grows four or five feet tall and produces a dozen or more pink flowers. When the species was discovered in 1927 there were only about 50 plants. Over the years the number dwindled, even though the conservancy acquired the site and maintained it as a secluded preserve.

By 1986, scientists funded by the U.S. Fish and Wildlife Service feared for the mallow's survival and tried to figure out why it was declining. Growth rings on nearby trees showed that long ago the area had been subject to frequent wildfires. In recent decades, however, fire prevention efforts had worked well. Perhaps too well: Like a few other species, the researchers suspected, the mallow's tough-coated seeds might not sprout until cracked open by the heat of fire.

Two years later they found some dormant seeds buried in the soil and heated them in the lab. The seeds opened, letting water in.

In May of 1992 the conservancy, along with state and federal foresters, lighted test grass fires over areas where newly shed mallow seeds lay on the ground. A few seeds sprouted and grew. A second burn this past spring resulted in about 500 seed sprouting.

"This shows us that simply setting aside land to protect rare or endangered species does not necessarily guarantee their protection," said Nature Conservancy President John Sawhill. "The remarkable comeback of Peter's Mountain mallow through the use of prescribed burning demonstrates the important role that this type of land management tool plays."

Comments Submitted to the Environment and Natural Resources Sub-Committee re: Medicinal Uses of Plants & Their Protection Under the Endangered Species Act

by

Roy Upton, Herbalist

on behalf of:

American Herbalists Guild
Box 1683 • Soquel, Ca. • 95073
Tel/FAX: 408-462-2441

November 9, 1993

Introduction to the American Herbalists Guild

The American Herbalists Guild (AHG) is the only peer review, professional association of medical herbalists in the United States. Our primary goal is to actively help develop and foster a high level of education, proficiency, skill and ethics among herbalists. Part of our mission statement includes the promotion of an ecologically environment and to increase awareness concerning the inter-dependence of all life, especially the plant-human relationships.

To help fulfill this goal, the American Herbalists Guild participated in a survey of medical herbalists nationwide in developing a list of medicinal plants that can be substituted for plants that are more sensitive. A future project is the development of the Extra Pharmacopoeia which will be a compendium of little-used, but commonly available herbs that will help likewise lessen the burden on sensitive species . We also are concerned with the impact of harvesting on native stands. Whereas a skilled and experienced "wildcrafter" can actually increase the proliferation of plant populations, an inexperienced or insensitive gatherer can destroy plant populations. However, destruction of habitat is far and away the most serious threat to native plant populations, and more serious consideration must given with regards to the environmental impact of further development.

The AHG would also like to make this Committee of the little-acknowledged fact that human life and human health is inextricably interwoven with environmental well-being. Like plants, humans are simply another part of the greater ecosystem of the planet. However, unlike the plants and most other living organisms, humans provide nothing that the earth needs for her survival, but rather are completely dependent on her resources. Humans have yet to realize the long-term consequences of our environmentally-destructive actions. Excessive development, and loss of species diversity today can have negative effects that may take decades to recognize and generations to reverse, if the damage can be reversed.

Plants as Medicines

Many people do not realize that more than 50% of modern pharmaceutical drugs had their origins in plant materials, and though only a fraction of all the species of plants have been examined, humankind has already reaped enormous benefits. Pharmaceutical manufacturers continue to rely on crude plants for the processing of drugs such as estrogenic and progesterenic drugs from the Mexican Wild Yam *Dioscorea spp.*, and more recently Taxol from the Northwestern Pacific Yew *Taxus spp.* As the natural habitats for these herbs disappear, and the plants become harder to obtain, the costs of the material rises dramatically.

Though we acknowledge that there is a distinct importance in preserving plant species and their ecosystems for their own inherent value, in contrast to simply preserving them for what they can contribute to society, we also acknowledge that it is important, in an economically-driven society, to provide a strong case that shows there are economic benefits as well.

IMPORTANCE OF PLANT-DERIVED DRUGS

- **WHO estimates that 80% of the world's population relies chiefly on traditional medicine.**
- **A major part of traditional therapies involves the use of plant extracts or their active constituents.**
- **25% of all prescriptions sold in the USA between 1959 and 1980 contained extracts or active principles of higher plants.**
- **Consumers in 1980 in the USA paid more than $8 billion for prescriptions containing active principles obtained from plants.**
- **WHO/WFPMM study confirms world-wide importance of herbal medicines.**

While the contributions that plants make to modern pharmacy are clear, there is little acknowledgment, within the society as a whole, of what these plants can contribute when used as traditional herbal medicines. Virtually every nation worldwide, with the exception of the United States and Canada, acknowledges the immense value medicinal plants contribute to health care. Most European and all Asian countries have mechanisms by which the benefits of traditional herbal medicines can be used within the public health care system. Not only are these traditional medicines openly embraced, in many cases they are reimbursed under the national insurance programs.

For the past two decades, the World Health Organization has stated that the majority of the world's population continues to rely on traditional herbal medicines as a primary source of medicine. In 1992, WHO published a Guidelines For The Assessment of Herbal Medicines which is a document that addresses the importance, as well as ways of integrating herbal medicines into the fabric of a nation's health care delivery system. In this document they state:

"The success of any health system depends on the ready availability and use of suitable drugs on a sustainable basis. Medicinal plants have always played a key role in world health...They offer local populations and others immediate access to safe and effective products for use in the treatment of illness through self-medication. Only a fraction of the world's plants have been studied, yet humankind has already reaped enormous benefits. Perhaps the most important role for WHO is to ensure that traditional plant remedies are neither accepted outright nor blankly rejected, but rather examined critically and with an open mind."

Tantamount to this, in another similar action, the WHO in conjunction with other plant conservation groups met in Chiang Mai, Thailand for the International Consultation on Conservation of Medicinal Plants. The focus of this conference was to re-affirm the important contributions that medicinal plants provide in helping WHO achieve its goal of "Health for All by the Year 2000" A World Conservation Strategy was established with the following proclamation.

Chiang Mai Proclamation

WE:

• Recognize that medicinal plants are essential in primary health care, both in self-medication and in national health services;

• Are alarmed at the consequences of loss of plant diversity around the world;

• View with grave concern the fact that many of the plants that provide traditional and modern drugs are threatened;

• Draw the attention of the United Nations, its agencies and Member States, other international agencies and their members and non-governmental organisations to:

— The vital importance of medicinal plants in health care;
— The increasing and unacceptable loss of these medicinal plants due to habitat destruction and unsustainable harvesting practices;
— The fact that plant resources in one country are often of critical importance to other countries;
— The significant economic value of the medicinal plants used today and the great potential of the plant kingdom to provide new drugs;
—The continuing disruption and loss of indigenous cultures, which often hold the key to finding new medicinal plants that may benefit the global community;
— The urgent need for international cooperation to establish programmes for conservation of medicinal plants to ensure that adequate quantities are available for future generations.

We, the members of the Chiang Mai International Consultation, hereby call on all people to commit themselves to Save the Plants the Save Lives.

Chiang Mai, Thailand
26 March, 1988

Environmental Preservation Through Medicinal Plant Propagation

Organizations such as the Rainforest Alliance have been working with third-world nations in developing contractual agreements between private industry and local governments by which those governments can develop a sustainable source of income through the harvesting of medicinal plants. Such agreements can provide a sustainable economic base for the nation as compared to the one-time cost paid for clear-cut lumber. Through an active land

management program, the propagation of medicinal plants can provide similar economic incentives for preserving what is left of our own old-growth timber, wet-lands, forests and prairies. Consequently, such a new and diverse industry could potentially create tens-of-thousands of additional jobs just in the propagation, harvesting, processing and distributing of such products. Millions of additional jobs could be provided through the development of new markets. Until the U.S. takes an active role in developing such markets, we will be at a distinct disadvantage with regards to the trade and commerce of bulk medicinal plant supplies and finished medicinal plant products which detracts from our society's physical and economic well-being.

Economic Impact of Medicinal Plants

In 1980, the active constituents of medicinal plants used in the manufacture of pharmaceutical drugs accounted for more than $8 billion in the U.S. Similarly, enormous economic value is to be found in the commerce of traditional herbal medicines complementary to the conventional drug market. In a 1993 survey, it was estimated that the retail sales for herbal products in the U.S. exceeded $1.5 billion, and the majority of herbal companies have been experiencing an annual growth of 20%-35% for the past four years. This is extremely significant as this growth has occurred during one of the worst economic recessions in decades, and during a time when federal regulations have been antagonistic toward the commerce of herbal products. As public demand continues to increase, and legislative barriers against such medicines are modified, the potential for growth will increase exponentially.

The international market has similar potential. For example, in **Germany**, approximately 1/3 of the medicines available on the market are plant-based, and approximately 60% of all physicians dispense herbal medicines, contributing to a medicinal plants market in excess of $1 billion per year. Until 1991, the German traditional herb market had been importing as much as 45,000 pounds of the herb Echinacea angustifolia/pallida from America each year. However, due to inconsistent availability, the Germans have begun large-scale cultivation of the plant themselves. Thus America loses out on a cash crop of an herb that is only indigenous to North America.

In Longhua Hospital in **China**, four tons of herbs are dispensed in the pharmacies on a daily basis. This is only one of four such hospitals in Beijing. In **Japan**, herbal medicines are used by the majority of the population and there is a strong consumer demand for American products, including herbal products due to a belief that there is an inherent superiority in "Western" prepared products. In short, America is missing out on a multi-million, multi-billion dollar domestic and international market by not encouraging and subsidizing large-scale production of medicinal plant crops in the same way that other agricultural crops are. Organic

growers in Washington and Oregon are selling Echinacea roots for $13.00 per pound to manufacturers and grossing $9,333 per acre from Echinacea crops, and a range of from $5,000-$9,000 per acre for medicinal herbs in general. **Ginseng** diggers are getting $230 per pound for wild ginseng. Goldenseal sells for $30 per pound with approximately 65,000 pounds sold in 1992. Each of these botanicals are primary candidates for cultivation due to the decline of their natural habitats.

Strengthening the Endangered Species Act

The American Herbalists Guild strongly supports additional protection of sensitive, threatened or endangered plants under the Endangered Species Protection Act. Unfortunately, there are a wide array of parameters presently with regards to what level of "criticalness" a species is defined. There are Federal parameters, Fish and Wildlife have different parameters, the nature Conservancy has their own guidelines, while individual states have their own. We would like to make the following recommendations to this Committee.

- Work toward developing a national forum in which the varying organizations can come together to discuss reforming the Endangered Species Act and the parameters by which sensitive, threatened or endangered species are defined.

- Strengthen current national protection standards that will provide meaningful protection for sensitive, threatened or endangered species.

- Realize the economic benefits associated with environmental preservation through the development of sustainable harvesting of medicinal plants both as modern drugs and traditional medicines.

- Act as a liaison to other Committees and Government Agencies in helping each to realize the importance of supporting the inclusion of medicinal plants into the health care delivery system.

- Work in concert with herbal organizations to develop national wild-crafting guidelines that reflect the environmental needs of a variety of bio-regions.

- Work toward establishing a permit system by which experienced wildcrafters could have access to national and state parks for the express purpose of gathering medicinal plants according to defined guidelines.

- Actively pursue avenues through other governmental agencies, such as the United States Department of Agriculture, by which the propagation of medicinal plants can be encouraged, thereby lessening the demand on wild populations.

- Recognize that destruction of habitats, and ecosystems have, by far, the greatest impact on native populations.

- Recognize that loss of habitat and species diversity can have long-term, potentially irreversible negative consequences that may not be recognized for decades.

- That strengthening of the Endangered Species Act has benefits and merits that extend far beyond the potential of what these species can contribute to human existence.

We are very concerned with the loss of habitat that is leading to the demise of many plant species. As everyone is aware, we are losing our prairies, wetlands, grass lands and old-growth ecosystems at an ever-increasing pace. However, most people do not realize that as these ecosystems are destroyed the potential for discovering new benefits of the medicinal plants that inhabit the area is also lost. We want to thank this Committee for its work in this area and will support these efforts in whatever way we can.

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